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LETTER TO THE EDITOR

Rapid diagnosis and initiation of treatment has a crucial role in the prognosis of primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive Non-Hodgkin lymphoma. Diagnosis of PCNSL is challenging and non-specific symptoms can lead to a delay in the diagnosis. After successful therapy, patients have excellent recovery potential and may reach a good quality of life. The data of 186 PCNSL patients diagnosed during 2003–2020 were analysed retrospectively. A significant correlation between disease-specific survival (DSS) and time from the first hospital visit to initiation of treatment was found ($p = 0.001$). Thus, patients suggestive of PCNSL should be diagnosed and proceed to therapy as a medical emergency. The awareness of PCNSL should be increased among all health care professionals.

Initiation of treatment is time sensitive for optimal neurologic recovery and disease control in PCNSL.[1] PCNSL is a rare and aggressive Non-Hodgkin lymphoma.[2,3] Several reports have described a growing incidence rate.[4] The prognosis of PCNSL has been dismal, but during recent years there has been considerable progress in treatment results.[5–10] Despite the chemo-and radiosensitivity, relapses are common and long-term survival remains suboptimal.[11] The current standard of therapy includes intravenous high-dose methotrexate-based multiagent chemotherapy, often combined with consolidative high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation.[12]

Diagnosis of PCNSL is challenging and non-specific symptoms can lead to a delay in the diagnosis.[1] The most common clinical symptoms of patients with PCNSL are non-specific neurocognitive deficits.[7] Most patients with PCNSL will present with focal neurologic deficits.[8] Almost half of the patients develop non-specific cognitive or behavioural changes. Signs of elevated intracranial pressure may also be seen in 33% of patients. Patients may also have lymphoma isolated to the vitreoretinal space, which causes limited to subtle visual abnormalities, such as blurring, decreased acuity, or floaters, but a majority of patients with PCNSL with ocular involvement have no visual symptoms.[9]

Magnetic resonance imaging (MRI) with gadolinium contrast is the most sensitive imaging modality in the diagnosis of PCNSL.[10] A slit-lamp evaluation coupled with multimodal retinal imaging to look for malignant cells in the vitreous humour or retina is needed to complete staging.[13] Diagnosis of PCNSL is confirmed by either neurosurgical biopsy from the tumour or positive spinal fluid or vitreal cytology or flow cytometry. Systemic lymphomas are excluded by 18FDG-PET. CT scan coupled with bone marrow and testis ultrasound should be considered if DFG-PET is not available. Intraocular lymphoma is diagnosed from vitreous fluid cytology or flow cytometry to look for malignant cells in the vitreous humour or retina is necessary to complete staging.[13] Due to the high proliferation rate of PCNSL, prompt diagnostics of PCNSL could be integral to a successful therapy as well as to preserving cognitive functioning. However, currently, there is scarce data exploring the impact of diagnostic delays on treatment outcomes.

We have retrospectively analysed the outcome of 186 PCNSL patients diagnosed during 2003–2020, concerning the correlation between times from the first hospital visit to the initiation of the treatment for the prognosis. Patients were treated with high-dose-methotrexate-based chemoimmunotherapy combined with rituximab ($n = 173$) in the first line (Table 1). Due to age, severe comorbidities, impaired ECOG (Eastern Co-operative Oncology Group) or declined cognitive performance status, 13 patients were referred only for radiotherapy. We evaluated time from the first hospital visit to the first radiographic imaging, diagnostics biopsies, and treatment initiations. Based on those time periods, we separated patients into two groups: group (A) time from first hospital visit to initiation of the treatment, 0–21 days, and group (B) time from first hospital visit to initiation of the treatment 22 days or more. We evaluated the effect of the diagnostic time period on the prognosis of the patients by using DSS data and Time to treatment Progression(TTP). The effect of the patient's initial symptoms on the time of the diagnostic process was analysed, and the impact of patient-specific factors such as age, gender, prognostics risk score according to Memorial Sloan-Kettering Cancer Center (MSCKK), eye involvement and ECOG status on diagnostics were evaluated. Risk groups were defined according to the MSKCC prognostic scoring system.[14] DSS was calculated from the date of the treatment initiation to the date of death from lymphoma. TTP was calculated from the date of treatment initiation to the date of last follow-up, lymphoma progression, or death due to lymphoma, whichever occurred first.

TABLE 1 Patient demographics.

Sex	*N* (%)
Male	107 (57.5)
Female	79 (42.5)
Age at the diagnosis	(Mean + SD)
Years	65.9 (14–89)
Performance status (ECOG)	*N* (%)
0	30 (16.1)
1	59 (31.7)
2	40 (21.5)
3	44 (23.7)
4	12 (6.5)
MSKCC risk group	*N* (%)
1 (age <50 years)	17 (9.1)
2 (age ≥50 years and KPS ≥70%)	77 (41.4)
3 (age ≥50 years and KPS <70%)	92 (49.5)
Eye involvement	*N* (%)
Yes	22 (11.8)
No	71 (38.2)
Missing data	93 (50.0)
ASCT	*N* (%)
Yes	41 (22.0)
No	145 (78.0)
Multichemotherapy	*N* (%)
Bonn/Nordic	75 (43.6)
MATrix	33 (19.2)
BBBD	33 (19.2)
Hd-MTX	26 (15.1)
Another non-specified regimen	5 (2.9)
Radiotherapy	*N* (%)
Yes	37 (19.9)
No	148 (79.6)
Missing data	1 (0.5)
Eye involvement	*N* (%)
Yes	22 (11.8)
No	71 (38.2)
Missing data	93 (50.0)
Symptoms present at diagnosis	*N* (%)
Speech production disorder	46 (24.7)
Sensorimotor disorder	67 (36.0)
Cognitive impairment	84 (45.2)
Headache	46 (24.7)
Epileptic seizure	23 (12.4)
Visual impairment	17 (9.1)
Another neurological symptom	88 (47.3)

Abbreviations: ASCT, autologous stem cell transplantation; ECOG, Eastern Co-operative Oncology Group; KPS, Karnofsky Performance Status; MSKCC, Memorial Sloan-Kettering Cancer Center.

The mean time from the first visit to MRI imaging was 8.0 (1–84) days, from MRI to biopsy 14.3 (0–85) days and from biopsy to the treatment initiation was 15.9 (1–84) days. The mean time of the whole process, starting from the first visit to the initiation of the treatment (TVIT), was 39.6 days (4–372) days. The median time for the treatment delay was 31.5 days. No statistically significant differences between hospitals were found in the diagnostic process. A significant correlation was found between DSS and TVIT ($p = 0.001$) based on the cut-off value of 21 days. Two- and 5-year DSS rates in group A (≤21 days) were 83.7% and 83.7% compared to 52.1% and 40.5% in group B (≥22 days), respectively ($p = 0.001$) (Figure 1A). Two- and 5-year overall survival values were both 68.7% in group A and 46.3% and 36% in group B, respectively. The respective 2- and 5-year TTP were 72.6% and 63.5% in group A and 54.2% and 39.6% in group B ($p = 0.044$; Figure 1B). Only speech disorders led to rapid imaging and initiation of the treatment. In our study, 46/186 (24.7%) of patients had some kind of speech disturbance. Correlation with other factors (age, gender, EGOC status and MSCKK score) had no effect on the patient's prognosis.

This study demonstrates the crucial impact of TVIT on disease control and the risk of PCNSL-associated death. After optimal treatment, PCNSL patients have excellent recovery potential and may reach a good quality of life[15]; however, long-lasting treatment side effects including cognitive impairment can be seen depending on the given treatments, and irreversible brain injury might have a major impact on quality of life. There is scarce research data on the effect of treatment delay on patients' recovery potential and quality of life after treatment. Our results of TVIT in disease outcome are in line with previous data.[16] The treatment delay was an independent risk factor for poor outcome in PCNSL. Delayed therapy led to decreased responses and outcomes.[16] Earlier study of Kaji et al. found a strong association between time period from biopsy-date to initiation of the treatment on treatment outcomes.[17] In our study there was also a trend towards significance in DSS ($p = 0.053$).

We found a significant correlation between patients´ speech disturbances and shorter TVIT. Accurate information about the proportion of speech disorders in neurological deficiency symptoms has not been reported in previous studies. Because the symptom was obvious, it might have led to a faster reaction and further examinations. Based on the results, every patient with clinical findings suggestive of PCNSL should be diagnosed and proceed to effective therapy as a medical emergency. The awareness of this rare disease should be increased among all health care professionals.

The retrospective setting leaves room for biases. However, we collected a moderate-sized multicentre data. These results should be verified in larger and presumably prospective settings in the future.

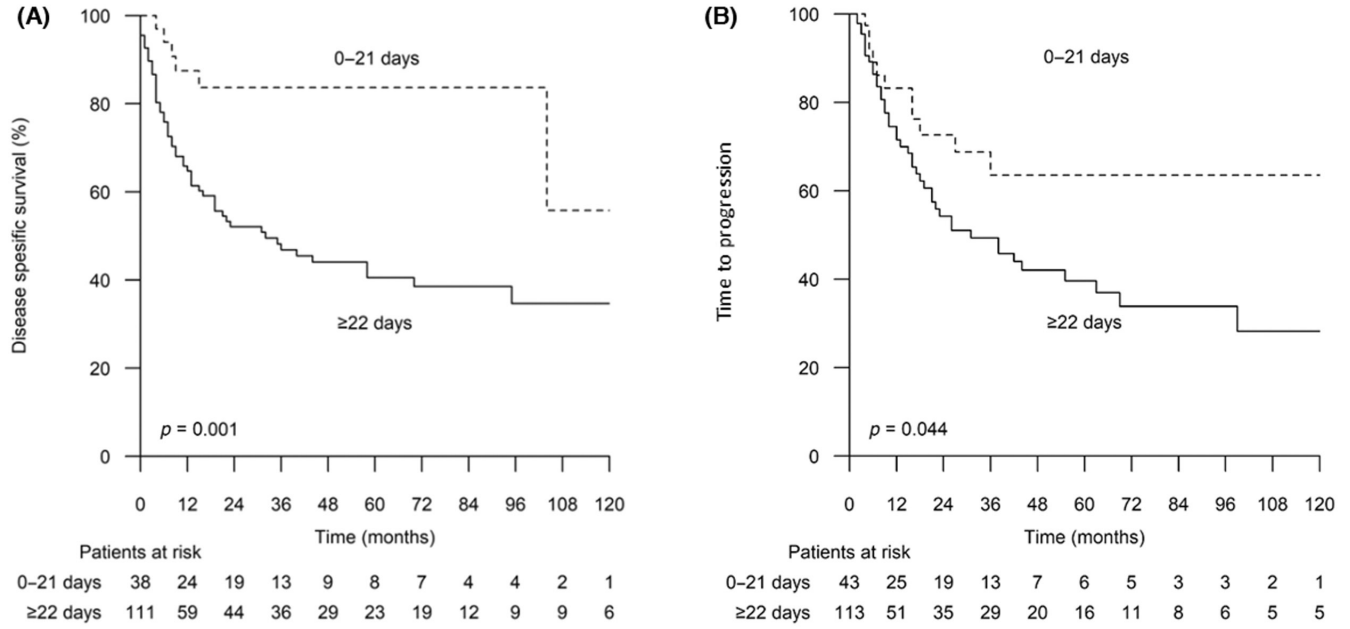

FIGURE 1 (A) Disease-specific survival based on treatment delays. Two- and 5-year disease-specific survival rates in group (A) (≤21 days) were 83.7% and 83.7% compared to 52.1% and 40.5% in group B (≥22 days). The difference was statistically significant ($p = 0.001$). (B) Time to treatment Progression (TTP) based on treatment delays. Two- and 5-year TTP were correspondingly 72.6% and 63.5% in group (A) and 54.2% and 39.6% in group (B) The difference was statistically significant ($p = 0.044$).

AUTHOR CONTRIBUTIONS

Conceptualization: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Methodology*: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Software*: Hanne Kuitunen, Inka Puhakka, Tuomas Selander and Outi Kuittinen. *Validation*: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Formal Analysis*: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Investigation*: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Resources*: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Data Curation*: Hanne Kuitunen, Inka Puhakka and Outi Kuittinen. *Writing—Original Draft Preparation*: Hanne Kuitunen and Inka Puhakka. *Writing—Review and Editing*: Hanne Kuitunen, Inka Puhakka, Aino Rönkä, Tuomas Selander, Pekka Jäkälä, Ulla-Mari Arkko, Tuula Klaavuniemi, Kaisa Sunela, Aino Rajamäki and Outi Kuittinen. *Visualization*: Hanne Kuitunen and Tuomas Selander. *Supervision*: Outi Kuittinen. *Project Administration*: Hanne Kuitunen. *Funding Acquisition*: Hanne Kuitunen and Outi Kuittinen All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the ethics committee of the Northern Ostrobothnia welfare region.

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