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Meningeal dissemination in primary CNS lymphoma: diagnosis, treatment, and survival in a large monocenter cohort

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The frequency of meningeal dissemination (MD) in primary CNS lymphoma (PCNSL), its prognostic impact, and optimal management have not been defined thus far. In 69 of 92 (75%) immunocompetent patients, primarily diagnosed with PCNSL at our institution between January 1994 and February 2007, cerebrospinal fluid was analyzed for MD. MD was found by cytomorphology in 7/63 (11%), by immunophenotyping in 1/32 (3%), and by PCR of the IgH CDR III region in 6/37 (16%). Neuroradiologic examination revealed MD in 3 of 69 patients (4%). Median event-free survival (EFS) of patients with MD diagnosed by any of the methods was 26 months, of those without MD 34.1 months ($P = .24$); median overall survival (OAS) of these two patients' groups was 45.5 and 42.5 months, respectively ($P = .34$). Patients with cytomorphologic proof of MD had a median EFS of 15.4 months and OAS of 18.5 months, those without MD 34.3 and 45 months ($P = .018$ and .017, respectively). We found a low frequency of MD despite the use of putatively sensitive diagnostic methods. No impact on outcome was seen for MD, diagnosed by any of the methods used; however, patients with cytomorphologic proof of MD had a significantly shorter median EFS and OAS.

Keywords: cerebrospinal fluid, CNS lymphoma, meningeal dissemination, prognosis

The incidence of meningeal dissemination (MD) in primary CNS lymphoma (PCNSL) is not exactly known. In 7%–42% of PCNSL patients, MD has been reported to be diagnosed by morphologic cerebrospinal fluid (CSF) assessment,[1–3] which is considered the gold standard in detecting MD in malignant disease.[4] In malignant lymphoma, however, a high rate of both false-negative and false-positive results has been reported.[5,6] False-negative results can be attributed to the paucity of tumor cells, frequently due to an upfront use of corticosteroids, and might be reduced by larger sample volumes, repeated sampling, and avoiding corticosteroids until definite diagnosis when possible.[4,7] The misinterpretation of reactive CSF lymphocytes as lymphoma cells, leading to false-positive results, represents another obstacle for the cytomorphlogic detection of lymphoma cells in the CSF.[8–10]

The optimal therapy of MD in PCNSL has not been established due to the rarity of the disease and the lack of adequately designed prospective trials. Moreover, the evaluation of the prognostic impact of MD has yielded conflicting results. In one study an inferior outcome was observed after deleting intrathecal chemotherapy from a combined systemic/intrathecal chemotherapy regimen.[11] These data raise the possibility of occult meningeal spread in many PCNSL patients. Addressing the meningeal compartment by intrathecal chemotherapy might improve the outcome of these patients. However, intrathecal chemotherapy bears the inconvenience of repeated lumbar punctures, the risk of an Ommaya reservoir infection,[12] and the increased risk of neurotoxicity.[13]

An optimal diagnostic CSF work-up including putatively sensitive methods such as immunophenotyping and PCR of the CDR III region of the rearranged IgH genes could help improve diagnostic accuracy for MD detection in PCNSL to ensure optimal management while omitting unnecessary treatment. Thus, we retrospectively evaluated all our immunocompetent PCNSL patients for incidence of MD diagnosed with different methods and assessed the therapeutic management and the impact of MD on survival.

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Methods

Patients and Treatment

Records of all 92 consecutive immunocompetent patients diagnosed with PCNSL or its subtype primary intraocular lymphoma (PIOL) from January 1994 to February 2007 at our institution were reviewed, and 69 patients (75%) in whom CSF analysis by at least one method capable of detecting lymphoma cells (cytomorphology, immunophenotyping, or PCR of the rearranged IgH gene CDR III region) was performed at first diagnosis were identified (in two further patients CSF was analyzed for cell count and protein only). The diagnosis of PCNSL/PIOL had to be confirmed histologically by tumor biopsy and/or cytologically from CSF or aqueous humor (in case of leptomeningeal involvement or ocular involvement, respectively). In rare cases where biopsy was not feasible or inconclusive, a strong suspicion of PCNSL based on radiomorphological and clinical features after exclusion of other conditions was accepted if treatment was started accordingly. Before treatment contrast-enhanced cerebral computed tomography (CT) scans or magnetic resonance imaging (MRI) of the brain with gadolinium, CSF analysis by a single lumbar puncture, CT of the chest/abdomen/pelvis, bone marrow biopsy, creatinine clearance, and HIV testing were performed in all patients. Slit lamp examination of the eye was performed only in patients with ocular symptoms.

Patients were intended to be treated with high-dose methotrexate (HDMTX), depending on their performance status and organ function. Three regimens were used: from January 1994 to April 2000 HDMTX 1.5 g/m^2 i.v. over 24 hours on day 2, carmustine 80 mg/m^2 i.v. on day 1 and procarbazine 100 mg/m^2 p.o. on days 1–8, repeated every 4 weeks (BMPD [carmustine, methotrexate, procarbazine, dexamethasone] protocol);[14] from May 2000 to November 2006 HDMTX 4 g/m^2 i.v. over 4 hours on day 1 as monotherapy, repeated every 2 weeks for maximal 6 courses; and from December 2006 to February 2007 HDMTX 4 g/m^2 i.v. over 4 hours on day 1 and ifosfamide 1.5 g/m^2 i.v. over 3 hours on days 3–5. All patients additionally received dexamethasone 3×8 mg/day in the first course, and thereafter only if clinically indicated. HDMTX dose was adjusted to patients' creatinine clearance.[3] Intrathecal treatment was given only to patients on the BMPD protocol: 15 mg MTX on day 1 of each course to patients with cytomorphologic proof of lymphoma in the CSF and in course 1 only to all other patients. Treatment response was evaluated by MRI or CT after the first and third BMPD treatment course and in case of HDMTX monotherapy or HDMTX/ifosfamide combination treatment after the third and the sixth course. Sequential CSF evaluations during the course of treatment were not performed routinely, regardless of initial presence of MD. During the follow-up all patients were followed longitudinally with surveillance brain MRI or CT scans and neurologic examinations every 3 months in the first year, every 4 months in the second year and every 6 months thereafter. Additional neuroradiologic evaluation was performed upon clinical suspicion.

Survival data of 49 of the patients have been previously reported.[15]

CSF Analysis

CSF was obtained by lumbar puncture at first diagnosis of PCNSL prior to any chemo- or radiotherapy (excluding corticosteroids) and immediately processed for cell count, cytomorphology, and protein concentration. The CSF evaluation for MD included: cytomorphology in 63 patients, immunophenotyping in 32 patients (immunocytology in 4 patients and flow cytometry with fluorescent-amplified cell-sorting [FACS] analysis in 28 patients), and PCR of the rearranged IgH gene CDR III region in 37 patients. Additionally, CSF was evaluated for cell count in 64 patients and for protein in 55 patients.

Cytomorphology was interpreted by at least two experienced hematopathologists/neurologists, and was termed positive for conclusive detection of lymphoma cells and suspicious when atypical lymphatic cells not clearly diagnostic of malignancy were detectable; the remaining cases were termed negative.

For immunophenotyping, CSF was either centrifuged within 2 hours after asservation and spotted on poly-L-lysin-coated glass slides with subsequent antibody staining for CD19, CD3, lambda, and kappa chains[16] or measured by flow cytometry with 2- or 4-color staining of the same antigens. Immnunophenotyping was regarded positive when a monoclonal B-cell population (exclusive expression of lambda or kappa immunoglobulin light chains) was detected.

For molecular genetic analysis, the PCR of the rearranged IgH genes was performed as described recently until March 2006.[17] Briefly, a seminested PCR of the IgH chain CDR III region was performed using the primers LJH in the first, VLJH in the second, and FR3A in both PCR reactions. All samples were tested with a human growth hormone PCR to check for amplifiable DNA. All specimens were amplified at least twice in independent PCR runs to avoid false monoclonal interpretation of pseudomonoclonal rearrangement patterns.[18] From April 2006 on, samples ($n = 5$) were subjected to a PCR using 3 sets of family-specific *IgH* primers according to the BIOMED-2 protocol, which was modified to apply 50 instead of 35 cycles for increased sensitivity. Three different framework region primer sets (*FR1*, *FR2*, and *FR3*) were applied separately to all samples in conjunction with an IgH joining segment (*JH*) consensus primer (*JH*22).[19] In each PCR, positive (DNA from a B-cell line) and negative controls (sterile water) were included. A monoclonal pattern was defined as the detection of a single or dominating amplicon of identical size in repetitive experiments. Multiple peaks characterized polyclonality.

Elevated cell count was defined as $\geq 5/\mu$l, and elevated protein as >450 mg/l.

Neuroimaging

Brain MRIs were obtained before treatment in 58 patients and CT in 10 patients; in 1 patient imaging modality is unknown. All scans available ($n = 63$) were reviewed by an experienced neuroradiologist. All examinations included T1- and T2-weighted sequences as well as contrast-enhanced studies. Cerebral imaging was performed on various MR scanners with field strengths of 1.0–1.5 T. For the T1-weighted scans, all patients received 0.1-mmol gadolinium–DTPA per kg body weight. CT scans were performed as contrast-enhanced cerebral CTs. MD on neuroimaging was defined as contrast-enhancement of the leptomeninges.

Definition of MD

Patients were regarded having MD if at least one of the following conditions was fulfilled: conclusive cytomorphological detection of lymphoma cells, light-chain restricted B-cell population detected by immunocytology or flow cytometry, presence of a dominant amplicon in PCR analysis, or evidence of MD on MRI.

Statistics

For statistical analysis, patient characteristics were grouped according to prognostic factors previously published: age $\leq$50 and $>$50 years, age $\leq$60 and $>$60 years and age as a continuous variable, Karnofsky performance score $\geq$70 and $<$70, the MSKCC prognostic score,[20] and superficial and deep lesion location. Event-free survival (EFS) was defined as the time from histologic diagnosis to first documentation of relapse (on imaging or in CSF) or death from any cause in patients responding (complete response and partial response) to first therapy since the survival of non-responders and patients treated with steroids only is usually very short in PCNSL. Overall survival (OAS) was defined as the time from beginning of treatment to death from any cause, according to the standardized response criteria for non-Hodgkin's lymphoma.[21]

EFS and OAS were estimated by the Kaplan–Meier method. Group comparisons were made using the log-rank test. Distribution of patient characteristics to different groups was analyzed by the chi-square test. MD status and pleocytosis or elevated CSF protein concentration were compared by Fisher's exact test. Mean values of independent groups were compared with Student's *t*-test. The level of significance was .05 (2-sided). Commercially available statistical software was used (SPSS for Windows, release 14.0).

Results

Patient Characteristics

Of 69 patients with CSF analysis for MD parenchymal brain involvement was present in 66 (96%), isolated meningeal lymphoma (diagnosed by CSF cytomorphology) in 2 patients (3%) and isolated intraocular lymphoma in 1 patient.

In 6 patients diagnosis could not be established by conclusive histology or positive CSF/vitreous cytology, in two of these patients biopsy was not feasible due to lesion location, and in one patient clinical condition was too critical for biopsy. In another three patients biopsy was inconclusive showing non-specific reactive tissue. A probable diagnosis was then made on clinical (rapid onset of symptoms and response to corticosteroids) and radiologic features (proximity to the subarachnoid space, strong and homogeneous contrast enhancement, moderate edema, and absence of necrosis) and after exclusion of infectious diseases by serology and CSF analysis (e.g. herpes virus, cytomegaly virus, Epstein–Barr virus, HIV, JC virus, toxoplasmosis, mycobacteria, and cryptococci).

Concomitant ocular involvement was detected by slit lamp examination in 1 of 19 (5%) patients examined. Data on steroid exposure before MD evaluation was available for 23 (33%) patients; of those 13 (57%) were on steroids.

Characteristics of all patients and the comparison between patients with MD vs those without MD are given in Table 1. No statistically significant difference was observed between both groups for any parameter. Moreover, no significant difference was found for the MSKCC score.

Cerebrospinal Fluid

Lymphoma cells were found by cytomorphologic examination in 7 of 63 (11%) samples and suspicious lymphocytes in 4 samples (6%). Of the 32 samples evaluated by immunophenotyping, 1 (3%) was positive and 31 negative. Of the 37 samples with PCR analysis, 6 (16%) showed a monoclonal pattern, 24 (65%) a polyclonal pattern, and in 7 (19%) no DNA was amplifiable.

Based on the results of all methods together, 11 patients (16%) were regarded as having MD (Table 2).

While steroid medication was part of the initial treatment in all patients, information on concomitant steroid medication at the time of CSF sampling was available for 23 patients. Of those, 13 (57%) were on corticosteroids (2 of 5 with MD and 11 of 18 patients without MD).

Median CSF cell count was 5/μl (range, 0–237; $n = 64$) and median protein concentration of 760 mg/l (range, 93–4117; $n = 55$). An elevated cell count (5/μl) was found in 26 (41%) patients, an elevated protein level in 44 patients (80%). No significant correlation was found between proof of MD and CSF pleocytosis or elevated protein (Table 3).

Initial Treatment

Sixty-one patients (88%) received the intended HDMTX-based chemotherapy: 44 as monotherapy and 17 in combination with other cytostatics (ifosfamide, high-dose cytarabine, BCNU, and procarbazine).

Table 1. Patient characteristics

	Total, $n = 69$	Percentage	With MD, $n = 11$	Without MD, $n = 58$
Age (years)				
Median			62	61
Range			16–87	45–78
Sex				
Male	32	46	7	25
Female	37	54	4	33
Karnofsky index (%)				
≥ 70	45	65	8	37
< 70	21	30	2	19
Unknown	3	4	1	2
MSKCC score				
1	11	16	0	11
2	36	52	8	28
3	19	28	2	17
Unknown	3	4	1	2
Intracerebral lesion location				
No intracerebral lesion	3	4	2	1
Superficial lesion	36	52	6	30
Deep lesion	29	42	2	27
Unknown	1	1	1	0
Pathologic diagnosis confirmation				
Stereotactic biopsy	32	46	4	28
Partial tumor resection	19	28	3	16
Total tumor resection	6	9	0	6
Surgical procedure unknown	1	1	0	1
CSF only	4	6	4	0
Vitrectomy only	1	1	0	1
None	6	9	0	6
Histology				
No histology	8	12	4	4
DLCBL	52	75	5	47
T-NHL	1	1	1	0
Low-grade B-NHL	4	6	1	3
Inconclusive	3	4	0	3
Unknown	1	1	0	1

Abbreviations: MD, meningeal dissemination; MSKCC, Memorial Sloan-Kettering Cancer Center; MRI, magnetic resonance imaging; DLCBL, diffuse large-cell B-cell lymphoma; T-NHL, T-cell non-Hodgkin lymphoma; B-NHL, B-cell non-Hodgkin lymphoma.

Eight patients did not receive HDMTX-based chemotherapy due to poor physical condition or renal insufficiency: 2 received topotecan monotherapy, 3 steroids only, and 2 were treated with whole-brain irradiation (WBI). One patient with PIOL had vitrectomy and local irradiation only. Twelve patients treated with BMPD additionally received intrathecal treatment with methotrexate: 10 patients without cytomorphologic proof of MD in course 1 only and 2 patients with lymphoma cells in CSF in each course. In patients receiving HDMTX-based chemotherapy, 10 additionally had WBI as part of their initial treatment.

Nine of the 11 patients with MD received HDMTX-based therapy (2 of them with consecutive WBI), 1 patient had WBI only, and 1 patient received steroids only.

Table 2. Results of different methods for MD detection

	Cytomorphology			
	Negative ($n = 52$)	Positive ($n = 7$)	Suspicious ($n = 4$)	Not done ($n = 6$)
Immunocytology				
Positive	0	1	0	0
Negative	24	3	1	3
Not done	28	3	3	3
PCR				
Monoclonal	3	2	1	0
Polyclonal	17	1	2	4
DNA not amplifiable	6	0	0	1
Not done	26	4	1	1
Neuroimaging				
Positive	0	3	0	0
Negative	52	4	4	6

Table 3. CSF pleocytosis and protein concentration

	Number of patients	Number of patients with MD	OR (95% CI)	P value
CSF pleocytosis				
No	38	5	1.98 (0.53–7.34)	0.33
Yes	26	6		
Missing	5	–		
CSF protein				
Normal	11	1	1.58 (0.17–14.66)	1.0
Elevated	44	6		
Missing	14	4		

Abbreviation: OR, odds ratio.

Outcome

The median follow-up was 42.8 months (95% CI: 23.9–61.7). The median OAS of all patients with CSF analysis for MD was 42.5 months (95% CI: 33.4–51.6), and of those without MD was 23.8 months (95% CI: 0–65.8) ($P = .3$).

Of the 11 patients with MD, 7 responded to primary treatment, and had a median EFS of 26 months (95% CI: 4.3–47.7), and 4 progressed. Four of the 7 responders relapsed: 3 in the brain and 1 in the skin. Of patients

without MD, 34 responded to primary treatment with a median EFS of 34.1 months (95% CI: 26.2–42): 14 relapsed within the brain parenchyma and 1 patient each in the CSF, in the lung/mediastinal lymph nodes and in the testes. The difference in EFS of patients with MD vs those without was not significant ($P = .24$).

Median OAS of the 11 patients with MD (diagnosed by either of the methods) was 45.5 months (95% CI: 16.6–74.4) as compared with 42.5 months (95% CI: 33.8–51.2) in the 58 patients without MD ($P = .34$; Fig. 1).

Patients with cytomorphologic proof of MD ($n = 7$; Table 4) had a median OAS of 18.5 months (95% CI: 0–45.4), those with a negative or suspicious CSF cytomorphology ($n = 56$) of 45 months (95% CI: 38.7–51.3); this difference was significant ($P = .017$; Fig. 2). A significant difference between these groups was also found for median EFS with 15.4 months (95% CI: 0–36.5) vs 34.3 months (95% CI: 28.2–40.4 months), respectively ($P = .018$). No significant difference was found for MSKCC score between these groups.

With a median OAS of 52.9 months (95% CI: 40.5–65.3), patients with an elevated cell count in the CSF ($n = 26$) had a trend towards longer survival compared with patients with a normal cell count ($n = 8$) with a median OAS of 37.9 months (95% CI: 27.2–48.6; $P = .095$). No significant OAS difference was found for patients with elevated vs normal CSF protein concentration.

Discussion

Our study population might have been selected by the referral bias, since patients in smaller community hospitals might not have received biopsy or not have been

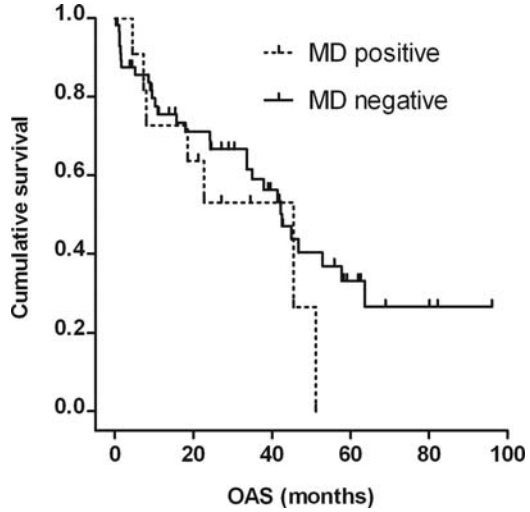

Fig. 1. Kaplan–Meier estimate of OAS for MD-positive ($n = 11$) and MD-negative patients ($n = 58$). Median OAS was 45.5 (95% CI: 16.6–74.4) months (7 events, 4 patients censored) and 42.5 (95% CI: 33.8–51.2) months (29 events, 29 patients censored), respectively. $P = .34$ (log-rank test).

Table 4. Characteristics of patients with cytomorphologic proof of MD in CSF

Age (sex)	Pathologic diagnosis	Disease localization on MRI	Primary treatment/response	Relapse (TTR, months)/salvage treatment/response	OAS (months)/cause of death
54 (f)	CSF cytology only	Brain	WBI/CR	Brain and CSF (2)/2× BMPD/CR	27.1 + /lost to follow-up
83 (m)	DLBCL	Meninges and brain	4× HDMT × /SD	Brain (4)/WBI/PD	18.5/lymphoma
70 (f)	DLBCL	Brain and meninges	3× BMPD + WBI/CR	–	4.5/neurotoxicity
74 (f)	T-NHL	Brain	Steroids only/PD	–	7.3/lymphoma
64 (m)	CSF cytology only	Meninges	2× BMPD + 2× HDMTX/CR	Cutaneous (28)/6× CHOP/CR Second relapse lung and tonsils/1× ICE/unknown	45.5/sepsis on therapy
62 (f)	DLBCL	Brain	2× HDMTX/PD, 1× HD-AraC/PD WBI/PD	–	8.0/lymphoma
76 (m)	CSF cytology only	Brain	6× HDMTX + 2× HD-AraC/CR	Brain and CSF (16)/4× HDMTX + Ifosfamide/PR	22.7/lymphoma

Abbreviations: TTR, time to relapse; OAS, overall survival; f, female; m, male; CSF cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; T-NHL, T cell Non-Hodgkin's lymphoma; HDMTX, high-dose methotrexate; WBI, whole-brain irradiation; BMPD, carmustine, methotrexate, procarbazine, dexamethasone and 1× 15 mg MTX intrathecally in each course; CHOP, cyclophosphamide, adriamycin, vincristin, prednisolone; HD-AraC, high-dose cytarabine; ICE, ifosfamide, carboplatin, etoposide; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

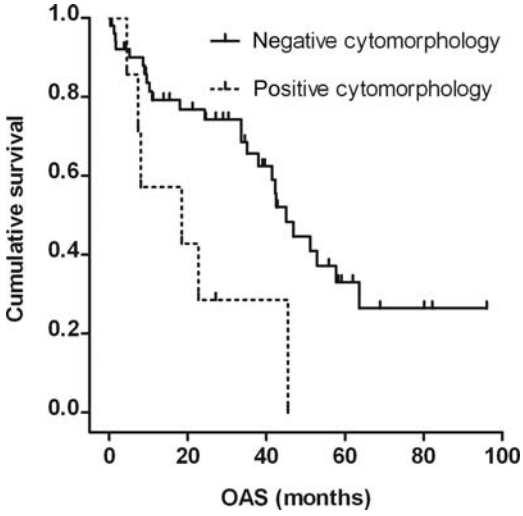

Fig. 2. Kaplan–Meier estimate of overall survival for patients with positive cytomorphology ($n = 7$) and patients with negative or suspicious cytomorphology ($n = 56$). Median OAS was 18.5 (95% CI: 0–45.4) months (6 events, 1 patient censored), and 45 (95% CI: 38.7–51.3) months (27 events, 29 patients censored), respectively. $P = .017$ (log-rank test).

referred to our institution due to poor physical condition, and a selection bias, because patients in poor condition might not have been subjected to lumbar puncture. This hypothesis is supported by a considerably poorer OAS of patients without CSF analysis for MD, although the difference is not statistically significant, probably because patient numbers were too small.

In this study, an extended diagnostic work-up was used, and MD was defined by a positive result of any of the methods used, although, in the absence of a reliable diagnostic "gold standard", their equivalence for MD detection in lymphoma can only be assumed. The frequency of MD found is in the lower range of frequencies reported in studies usually using the cytomorphologic examination only, ranging from 7%–42% (Table 5). Underestimation due to a singular puncture and a prior use of steroids in more than half of all documented patients can be assumed in our cohort; however, these limitations also apply to the majority of other studies. MD was detected with an equal frequency in patients with and without prior steroid use in our study, but the number of patients might have been too low to detect a significant difference.

The very low frequency of MD detection by immunophenotyping in this study is remarkable. A monoclonal B-cell population was found only in 1 of the 4 cytomorphologically positive samples evaluated by immunophenotyping. Small cell counts and rapid cell decay in a delayed analysis are major limitations of this method. However, a higher sensitivity of immunocytology as compared with cytomorphology for MD detection in hematologic malignancies primarily localized outside the CNS is suggested in the literature. In 3 small studies comparing flow cytometry with conventional cytomorphology, a much higher frequency of MD found by immunophenotyping was reported.[22–24] In the largest study investigating 51 newly diagnosed aggressive B-cell lymphomas with risk for CNS involvement, MD was detected more than twice as frequently using flow cytometry compared with conventional cytomorphology.[25]

The high rate of discordant cytomorphologic and PCR results is another striking finding in this study. Of 3 cytomorphologically positive samples evaluated by PCR, only in 1 a monoclonal PCR product was found. Conversely, only 1 of 6 samples with a monoclonal PCR product was positive on cytomorphologic examination, and 1 was regarded suspicious. False negatives in PCR can be explained by a high mutational frequency of PCNSL as compared with nodal diffuse-large B-cell lymphomas due to the introduction of further point mutations after immunoglobulin gene rearrangement, which can prevent annealing of PCR primers.[26,27] On the other hand, a misinterpretation of a peak caused by a single B-cell as a monoclonal population ("pseudomonoclonality") may result in a false-positive PCR. This can be minimized to some extent by repeated PCR in independent runs. However, the presence of false-positive cytology results cannot be finally ruled out. A high rate of discordant cytomorphologic and PCR results has also been reported in two other studies.[17,28] In a smaller study by Ekstein et al.,[29] 9 of 15 PCNSL patients with active disease had positive PCR results (60%); however, multiple samples from single patients during the course of disease, including relapse, were included in the evaluation.

The rate of MD detection by neuroradiologic evaluation was very low in our study. All these patients also had positive CSF findings. This corresponds to the data published by others who found the sensitivity of radiological methods for detection of MD in lymphoma lower than in solid tumors.[30,31] It cannot be excluded, however, that a higher detection frequency would have been found with an additional spinal imaging.

The prognostic impact of MD in PCNSL has not been defined yet. Blay et al.[32] found a trend towards worse survival in patients with a cytomorphologic proof of MD as compared with those without, whereas no impact of MD on survival was found by others.[2,7,14,20] The outcome of our patients with MD (diagnosed by either of the methods) was comparable to that of patients without MD with no differences in the relapse pattern between the two groups, but the power of our study was clearly limited by the relatively small number of patients. In the framework of our study, we could have detected a difference in median OAS of more than 3 years with 80% power. However, we saw a difference of only 3 months, which at least indicates that MD as defined in this study is not an important predictor of survival in PCNSL when treated with HDMTX. Remarkably, patients with cytomorphologic evidence of lymphoma cells had a significantly poorer outcome than those without. This may indicate a stronger prognostic impact of conventional CSF diagnostics, possibly detecting a higher tumor burden as compared

Table 5. Studies (more than 40 patients) reporting frequencies of MD in PCNSL

Author	Patients with CSF/all patients	% MD positive	Diagnostic methods (% positive)	Prior steroid use	Prognostic impact on OAS
Abrey et al.[20]	279/338	17	Cytomorphologic examination	Not reported	No impact
Ferreri et al.[2]	241/378	18	Cytomorphologic examination	Not reported	No impact for cytomorphologic proof
					Negative impact for CSF protein >450 mg/l
Blay et al.[32]	157/226	16	Cytomorphologic examination	Not reported	Negative impact for CSF protein >600 mg/l and positive cytomorphology (univariate)
Fischer et al.[33]	116/145	18	Cytomorphologic examination	71/91 with available data	Not evaluated
Balmaceda et al.[7]	86/96	42	Cytomorphologic examination (27%), imaging, meningeal biopsy	56/69 with available data	No impact
DeAngelis et al.[34]	81/98	21	Cytomorphologic examination	Not reported	Not evaluated
Gleissner et al.[17]	76/76	16	Cytomorphologic examination (8%), CDR III PCR (11%)	60/68	Not evaluated
Present study	69/92	16	Cytomorphologic examination (11%), immunophenotyping (3%), CDR III PCR (16%)	13/23 with available data	Negative impact for positive cytomorphology only
Pels et al.[12]	58/65	12	Cytomorphologic examination	Not reported	Not evaluated
Gavrilovic et al.[35]	57/57	18	Cytomorphologic examination	Not reported	Not evaluated
Abrey et al.[36]	52/52	21	Cytomorphologic examination	Not reported	Not evaluated
Hoang-Xuan et al.[37]	50/50	18	Not reported	Not reported	Not evaluated
Korfel et al.[14]	45/60	18	Cytomorphologic examination	Not reported	No impact
Poortmans et al.[38]	43/52	16	Not reported	Not reported	Not evaluated
O'Brien et al.[39]	42/46	7	Cytomorphologic examination, immunophenotyping	Not reported	Not evaluated

Abbreviations: OAS, overall survival; CSF, cerebrospinal fluid.

with the subclinical MD detection by putatively more sensitive methods.

In some studies, CSF protein concentration has been suggested to be an independent prognostic factor,[2,32] whereas no prognostic role has been reported by others.[20] In our study, no influence of CSF protein concentration on patients' outcome has been found.

Within limitations mentioned above, the diagnostic yield for MD detection in newly diagnosed PCNSL seems not improved by CSF immunophenotyping and MRI as compared with CSF cytomorphology. The value of a positive PCR result remains unclear since only a positive cytomorphologic result had an impact on outcome. Thus, considering cytomorphology a diagnostic gold standard for diagnosing MD in PCNSL seems still justified. These findings need to be confirmed by a prospective analysis of a larger patient cohort.

Conflict of interest statement. None declared.

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