Review Article

The Diagnosis and Treatment of Primary CNS Lymphoma

An Interdisciplinary Challenge

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Summary

Background: Primary central nervous system lymphoma is a diffuse large B-cell lymphoma with exclusive manifestation in the central nervous system (CNS), leptomeninges, and eyes. Its incidence is 0.5 per 100 000 persons per year. Currently, no evidence-based standard of care exists.

Methods: This review is based on pertinent publications (2000–2017) retrieved by a selective search in PubMed.

Results: The clinical and neuroradiological presentation of primary CNS lymphoma is often nonspecific, and histopathological confirmation is obligatory. The disease, if left untreated, leads to death within weeks or months. If the patient's general condition permits, treatment should consist of a high-dose chemotherapy based on methotrexate (HD-MTX) combined with rituximab and other cytostatic drugs that penetrate the blood–brain barrier. Long-term survival can be achieved in patients under age 70 by adding non-myeloablative consolidation chemotherapy or high-dose chemotherapy with autologous stem cell transplantation (HD-AST) to the induction therapy. Clinical trials comparing the efficacy and toxicity of these two treatment strategies are currently underway. Consolidation whole-brain radiotherapy is associated with the risk of severe neurotoxicity and should be reserved for patients who do not qualify for systemic treatment. Some 30% of patients are refractory to primary treatment, and at least 50% relapse. In patients who are still in good general condition, relapse can be managed with HD-AST. Re-exposure to conventional HD-MTX–based polychemotherapy is another option, if the initial response was durable. The 5-year survival rate of all treated patients is 31%, according to registry data.

Conclusion: Current recommendations for the treatment of primary CNS lymphoma are based on only a small number of prospective clinical trials. Patients with this disease should be treated by interdisciplinary teams in experienced centers, and preferably as part of a controlled trial.

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Primary central nervous system lymphomas (PCNSL) are aggressive brain tumors. They are a form of extranodal non-Hodgkin lymphoma (NHL) with exclusive manifestation in the brain, leptomeninges, and spinal cord. Ocular involvement (vitreoretinal lymphoma) is seen in 10% of patients and leptomeningeal tumor spread is found in about 15% of patients (1–3). Only highly proliferative, diffuse large B-cell lymphomas without systemic manifestation are categorized as PCNSL according to the most recent WHO classification (4).

PCNSLs account for 2% to 4% of all primary brain tumors (5). The incidence is about 0.5/100 000 persons per year, with over-65-year-olds being more commonly affected and a rising incidence in this age group. Men are more commonly affected than women (sex ratio 1.35 : 1) (6, 7). Immunosuppression is one of the risk factors for PCNSL; in this situation, PCNSL is typically associated with Epstein–Barr virus (EBV) (8).

Even though the prognosis of PCNSL has significantly improved over the last decades (median survival improved from 2.5 to 26 months) (7) and intensive treatments can achieve long-term remission in young patients, no evidence-based standard of care exists. Treatment recommendations are based on retrospective case series and few larger prospective studies. Among older patients, highly effective treatments are often associated with serious adverse events and the prognosis in this age group is significantly less favorable with median survival rates between 7 to 19 months, regardless of treatment (7, 9).

PCNSL is a rare cancer that is easily overlooked in the differential diagnosis and that is managed differently from other brain tumors. We therefore set out to provide a summary of the currently available evidence on its diagnosis and treatment.

Methods

We performed a PubMed search for the years 2000–2017, using the search algorithm: “primary central nervous system lymphoma” AND/OR “pcnsl”; filters activated: “meta-analysis”, “systematic reviews”, “randomized controlled trial”, “guideline”, “clinical trial”, “abstract”, “humans”, “English”, “German”. The search yielded 1175 results. After evaluating the abstracts (LB), 85 high-quality sources, including

Figure 1: Cranial magnetic resonance imaging (cMRI) of a patient with primary CNS lymphoma (PCNSL). A cMRI scan of this 61-year-old female patient was obtained because of personality changes rapidly progressing over several weeks, dysarthria, and unsteady gait. It revealed a homogeneously contrast-enhancing PCNSL (T1 with contrast) with diffusion abnormality in the diffusion-weighted (DWI) sequences and hyperintensity in T2-weighted sequences

some older articles, were selected as relevant for our paper and included in our analysis on a consensus basis with the other authors.

Clinical signs and symptoms

The signs and symptoms of PCNSL are nonspecific and rapidly progressive. Frequently (50–70% of cases), patients present with personality changes and cognitive impairments; in addition, 50% of patients experience focal neurological deficits. Signs and symptoms of increased intracranial pressure are less commonly observed at the time of diagnosis. These include headache, nausea, decreased alertness, seizures or, in case of vitreoretinal involvement, ocular symptoms (vitreous floaters, visual impairment).

Although leptomeningeal involvement is usually asymptomatic, it may trigger headache, neck or back pain and radicular symptoms (1, 8).

Imaging studies

Contrast-enhanced cranial magnetic resonance imaging (cMRI) is the most useful imaging modality (2, 10); however, nonspecific findings are not uncommon. It reveals unifocal or, in 35% of patients, multifocal, mainly supratentorial periventricular space-occupying lesions. Contrast enhancement is intense and generally homogeneous, but in 6% to 17% of patients inhomogeneous or missing (<2%) (10, 11). Typically, PCNSLs show significant diffusion restriction due to cell density

and appear hypointense on T2-weighted imaging and iso-/hypointense on T1-weighted imaging (10, 11) (Figure 1). Regions of the brain with normal imaging morphology are usually also involved (12).

Differential diagnosis

Imaging alone does not allow reliable discrimination from other malignant brain tumors (CNS metastasis, malignant glioma) or space-occupying inflammatory lesions (multiple sclerosis, sarcoidosis, vasculitis), more rarely of infectious nature (abscess, opportunistic CNS infections and toxoplasma encephalitis, progressive multifocal leukoencephalopathy) (3, 10); therefore, PCNSL should always be included in the differential diagnosis of space-occupying lesions of the brain. Regression of clinical and imaging findings of variable duration (usually weeks to months, rarely longer) is observed under steroid treatment in 40% to 80% of cases (13, 14). The histological picture is dominated by nonspecific inflammatory and reactive changes, while tumor cells are missing (3, 15). Therefore, in patients with suspected PCNSL, steroid treatment should be avoided before biopsies for histology have been taken.

Confirmation of diagnosis

Histopathological confirmation of the diagnosis is essential and should be sought without delay, given the aggressive course of the disease (2). Confirmation is typically achieved by stereotactic serial biopsies which are associated with a low peri-interventional risk for the patient (16). In the case of leptomeningeal or ocular involvement, lymphoma cells can only rarely be detected in the cerebrospinal fluid (CSF) or in the vitreous body aspirate using (immuno)cytological, flow cytometric or molecular biology methods. However, the latter does not allow definite classification of the lymphoma according to the WHO criteria which require immuno-histochemistry for confirmation (4). Currently, diagnostic biomarkers (proteins, RNA, DNA) in the cerebrospinal fluid do not play an established role in clinical routine (17).

In case steroid treatment was started before histology samples were obtained, the medication should be tapered off as soon as possible and then biopsies should be taken, because the diagnosis can only be established in 50% to 85% of patients under steroid treatment (15, 18). However, in case of persisting contrast enhancement and a rapidly progressive clinical course or threat to the patient's life, the biopsy should not necessarily be delayed. In case of inconclusive findings, imaging follow-ups should be performed at close intervals to ensure that patients showing signs of progression undergo a re-biopsy (2).

Diagnosis

If a PCNSL is diagnosed, it is recommended to perform a standardized diagnostic evaluation (Figure 1) (19). In addition to spinal tap and ophthalmological examination, patients should undergo whole-body computed

FIGURE 2

Diagnostic algorithm for suspected primary CNS lymphoma (PCNSL).

ADC, apparent diffusion coefficient; cMRI, cranial magnetic resonance imaging; CSF, cerebrospinal fluid; CT, computed tomography; Echo, transthoracic echocardiography; ECOG PS, Eastern Cooperative Oncology Group Performance Scale; IELSG, International Extranodal Lymphoma Study Group; LDH, lactate dehydrogenase; PET, positron emission tomography; PCNSL, primary CNS lymphoma; T1, T1-weighted sequence; T2, T2-weighted sequence; (adapted from Ferreri et al. 2011 [e47])

tomography (CT), or positron emission tomography CT (PET-CT), to rule out any systemic manifestation which is found in 10% of patients with cerebral lymphoma (20).

Additionally, the guidelines recommend a bone marrow aspiration to rule out bone marrow involvement, even though it does not change the treatment approach and may be dispensable (21).

Since more than 80% of patients with isolated vitreoretinal lymphoma develop CNS involvement over the course of the disease, cMRI and spinal tap should always be performed. In all patients, clinical chemistry testing (liver and kidney function tests), HIV testing, and hepatitis serology should be undertaken (19).

Histopathology and molecular pathophysiology

PCNSLs are mature B-cell lymphomas characterized by the expression of pan B-cell markers (CD20 and CD79a) (Figure 2). Typically, they have a high proliferation rate (Ki-67 proliferative index >70%). The tumor cells express germinal center markers, predominantly BCL6 and MUM1/IRF4, but no plasma cell markers (CD38, CD138). They show light-chain restriction and express IgM, but not IgG (22). Frequently,

B-cell receptor, Toll-like receptor and NF-κB signaling pathways are activated by changes in regulating genes (23–25), stimulating the proliferation of lymphoma cells and preventing their apoptosis.

Prognosis

PCNSLs are highly malignant lymphomas with a median survival of weeks to months if treatment is only symptomatic; however, with anticancer therapy 5-year survival is 31% (6). Old age and poor clinical performance status have the strongest negative impact on prognosis; besides these, increased LDH levels, elevated CSF protein levels, and involvement of deeper brain regions are summarized in the International Extranodal Lymphoma Study Group (IELSG) score (Figure 2) and associated with a poorer prognosis. In low-risk patients, the 2-year survival is 80%, in moderate-risk patients 48%, and in high-risk patients only 15% (26).

Management

Available study data

PCNSL is sensitive to radiation and chemotherapy. Due to the low incidence of PCNSL, it is challenging to conduct large randomized studies. The current treatment

Therapeutic algorithm for histologically confirmed primary CNS lymphoma (PCNSL) ECOG, Eastern Cooperative Oncology Group Performance Scale; HD-ASCT, high-dose chemotherapy with autologous stem cell transplantation; HD-MTX, high-dose methotrexate (≥ 3 g/m² body surface area over 4 hours).
* if in excellent general condition

FIGURE 3

recommendations are based on a few prospective treatment studies (Figure 2 and 3, Table). Given the heterogeneity of these studies, the small sample sizes, and the different endpoints, these studies are difficult to compare.

Surgical resection

A subgroup analysis of the largest PCNSL study conducted so far indicated that tumor resection may improve progression-free survival in patients with single PCNSL lesions (27). However, involvement of deeper brain structures, which is a contraindication for resection, is associated with a poorer prognosis and this was not taken into account. Thus, there is no established role of resection in the management of infiltrative PCNSL (2, 28).

Pharmacotherapy

The first-line treatment for PCNSL is systemic chemotherapy. Chemotherapy regimens for the treatment of systemic lymphoma are ineffective in PCNSL as these drugs do not readily pass the blood–brain barrier. Based on the currently available data, the following treatment strategies can be recommended:

High-dose methotrexate (HD-MTX; ≥ 3 g/m² body surface, given as a 4-hour IV infusion) is the most effective single active agent and a key component of all combination regimens (2). Outside of clinical trials and without subsequent consolidation, HD-MTX-based polychemotherapy should be administered over at least 6 cycles together with adequate supportive care (hydration, urine alkalinization, leucovorin rescue, and monitoring of MTX levels) (2).

HD-MTX monotherapy achieves complete remissions in only 30% to 40% of patients and is comparatively well tolerated (moderate toxicity in

<10% of cases) (29, 30). Adverse events include renal failure, blood count abnormalities, liver function abnormalities, pneumonitis, mucositis, and, in the long term, clinically relevant leukoencephalopathy, especially in older patients (31).

Combination chemotherapies with other cytostatic agents capable of crossing the blood–brain barrier, for example high-dose cytarabine (HD-AraC), thiopeta or ifosfamide, increase the overall response rate along with increased toxicity, while treatment-associated mortality remains unchanged (30, 32).

Treatment response to HD-MTX/AraC was further improved by adding rituximab, an anti-CD20 antibody, to the regimen; however, the effect was only significant if thiopeta (MATRIX protocol, [eTable 2]) was also added (overall response rate: 53% versus 74% versus 86%). Even though hematologic adverse events occurred more commonly in the intensified treatment arm, no significant differences were found with regard to the rate of serious infectious complications and treatment-associated mortality (33). However, a point of criticism is that only 54% of all patients reached the consolidation phase of the study. This was due to inadequate stem cell collection, prolonged adverse events, and neurological deterioration despite tumor regression, among others (34). The most commonly used protocols and currently recruiting studies are listed in the eSupplement and in eTable 1 and eTable 2.

Radiotherapy

In the majority of patients, percutaneous fractionated whole-brain radiotherapy leads to fast and usually complete remission; however, recurrences occur early. Median survival is only 12 to 18 months (35). With combined chemoradiotherapy, tumor control can be

significantly improved and—in prospective studies—median survival times of 31 to 90 months have been achieved (30, 36–40, e1). However, neurotoxicity occurring over a time course of months to years has emerged as a very serious problem. Affected patients show marked leukoencephalopathy, leading to cortical/subcortical atrophy and, in some cases, to severe cognitive deficits, gait abnormalities, incontinence, and need for nursing care (e2). The 5-year incidence of overt neurotoxicity is 12% to 65%; it is associated with mortality rates of 16% to 66% and primarily affects patients aged >60 years (30, 36–40, e1, e3–5). Delayed neurotoxicity is also observed in patients receiving intensive chemotherapy (e1, e6); however, extensive neurocognitive analyses showed that, especially irradiation, has a negative impact on cognitive performance and quality of life (e5, e7).

In the so far largest randomized phase III study, consolidation whole-brain radiotherapy did not improve overall survival compared to HD-MTX-based chemotherapy (e1). Thus, it should not be performed on a routine basis (1, 2).

Strategies to maintain long-term remission

Several strategies to intensify conventional chemotherapy have been evaluated in prospective studies, in some cases with promising results; they may be equally effective compared to chemoradiotherapy (34, e3).

Non-myeloablative consolidation chemotherapy achieved an efficacy comparable to that of chemoradiotherapy (median overall survival >59 months) (e8). Likewise, a HD-MTX-based polychemotherapy combined with intensive intraventricular chemotherapy via a reservoir (“Bonn protocol“, [eTable 2]) achieved long recurrence-free survival (>80 months), especially in younger patients (e9, e10). However, the regimen did not find widespread adoption due to the high rate of reservoir infections (19%). Without intraventricular chemotherapy, these good results could not be reproduced (e11). No controlled studies have yet been conducted to further explore the role of intrathecal treatment.

Lymphoma cells persisting in the CNS are reached by myeloablative, high-dose consolidation chemotherapy with autologous stem cell transplantation (HD-ASCT) as this strategy achieves very high drug levels in the CNS. The efficacy of HD-ASCT was evaluated in several phase II studies on younger patients without major comorbidities. In this selected patient population, HD-ASCT was a highly effective treatment option with curative potential (overall response 80–96%, median overall survival 64–104 months) (e12–14). More recent data indicate that HD-ASCT provides equal efficacy to consolidation whole-brain radiotherapy, but is associated with less neurotoxic adverse events (34). In prospective studies, HD-ASCT has been associated with a mortality of 0% to 12% (e13, e14), but, because of its toxicity, especially older patients are often not eligible for it. Thus, ongoing studies are evaluating an

Figure 4: Histology of the primary CNS lymphoma (PCNSL). Blast CD20-positive lymphoma cells infiltrate the brain parenchyma in a lawn-like pattern and spread, partly in groups, partly as solitary cells, in the brain tissue. The star marks a blood vessel with dense wall infiltration by small bystander lymphocytes. In the outer layers of the blood vessel wall adjacent to this layer, lymphoma cells are noted. Anti-CD20 immunohistochemistry, mild counterstaining with hemalum, original magnification $\times 200$

age-adapted HD-ASCT for patients aged >65 years (eTable 1). The value of the various consolidation strategies (non-myeloablative versus myeloablative) is being explored in randomized trials in Germany too (28, e15) (eTable 1). Until solid data have become available, no reliable conclusions can be drawn.

Management of recurrence

About one third of all PCNSL patients are primarily refractory to treatment and at least half of the patients with initial response to treatment experience a relapse (e16, e17). So far, no standard of care has been established for this situation; the majority of treatment recommendations are based on retrospective and a few prospective studies (28).

According to reviews, the overall response rates of recurrences range from 10% to 85%; however, remissions are short-lived (median progression-free survival [PFS] approx. three months) (28). In patients with long-lasting remission after initial treatment (median 24–26 months), re-exposure to HD-MTX-containing chemotherapy proved effective with a high response rate (85–91%) and a median survival of 41 to 62 months (e18, e19). For patients aged <65 years, promising data on HD-ASCT are available from the Freiburg ZNS-NHL study (2-year survival: 56%) which is now established in many German centers (e20) (eTable 2). With HD-ASCT, long-term remission was achieved even in cases with no response to HD-MTX-based induction (e20, e21). Other published regimens to treat recurrence include pemetrexed (e22), topotecan (e23), temozolomide in

TABLE

Studies on the first-line treatment of primary CNS lymphoma

Refer- ence	N°	Med. age (y)	Treatment protocol (induction → intensification / consolidation)	ORR (%)	Med. PFS (Mo)	Med. OS (Mo)
Conventional chemotherapy all age groups, N >40						
(e9) (e10)* ¹	65	62	HD-MTX, vincristine, ifosfamide, cyclophosphamide → AraC/vindesine → MTX + AraC icv	71	21 (TTP)	54
	30 (≤60 y)	52			64* ¹	>80* ¹
	35 (>60 y)				30* ¹	34* ¹
(e8)	44	61	Ritux, HD-MTX, TMZ → etoposide, AraC	77	29	> 59
(e43)	39 (≤65 y)	55	Ritux, HD-MTX, ifosfamide, cyclophosphamide → AraC, Vindesine → liposomal AraC isp	70	10 (DoR)	> 22
	27 (>66 y)	70	Ritux, HD-MTX, TMZ → AraC, vindesine → liposomal AraC isp Oral maintenance: TMZ for 12 months	81	>22 (DoR)	>22
Chemotherapy in older patients (>60 y), N >40						
(e6)	50	72	HD-MTX, procarbazine, lomustine → MTX + AraC icv	48	7	14
(e34)	95	72	HD-MTX+ TMZ	71	6	14
		73	HD-MTX + procarbazine, vincristine → AraC	82	10	31
(e33)	107	73	R, HD-MTX, procarbazine (lomustine) Oral maintenance: procarbazine	49	10	21
Chemotherapy + radiotherapy (RT), N >40						
(36)	102	57	HD-MTX, procarbazine, vincristine → RT	94	24	37
(37)	52	51	HD-MTX, teniposide, carmustine, MTX icv, AraC icv → RT	81	NA	46
(38)	56	60	HD-MTX, carmustine, procarbazine → RT	61	10	12
(30)	79	58	HD-MTX → RT	41	5 (FFS)	10
		59	HD-MTX + AraC → RT	69	9 (FFS)	31
(e1)	521 (318 per protocol)	61	HD-MTX, (ifosfamide) → AraC	54	12	37
			HD-MTX, (ifosfamide) → RT		18	32
(40)	52	60	Ritux, HD-MTX, procarbazine, vincristine → AraC + drRT	95	92	>70
(39)	53	57	R, HD-MTX, TMZ → drRT Oral maintenance: TMZ for 11 months	85	64	90
High-dose myeloablative therapy + autologous stem cell transplantation (HD-ASCT) ± RT, N ≥30						
(e12) (e44)* ¹	30	54	HD-MTX, AraC, TT → HD-ASCT (BCNU, TT) + RT	92	NS	>64 104* ¹
(e14)	32	57	HD-MTX, procarbazine, vincristine → HD-ASCT (busulfan, TT, cyclophosphamide)	96	not reached >84	>84
(e12)	79	56	R, HD-MTX → AraC, TT → HD-ASCT (BCNU, TT), RT (n = 10, only if no CR after induction)	80	74	>84
(33) (34)	75	58	MTX, AraC* ²	CR: 93	2y PFS: 75%	2y OS: 85%
	69	57	R, HD-MTX, AraC* ²			
	75	57	R, HD-MTX, AraC, TT* ²	CR: 95	2y PFS: 76%	2y OS: 71%

AraC, cytarabine; BCNU, carmustine; CR, complete remissions; DoR, duration of response; drRT, dose-reduced radiotherapy; FFS, failure-free survival; HD-ASCT, high-dose myeloablative therapy with autologous stem cell transplantation; HD-MTX, high-dose methotrexate; icv, intraventricular (via intrathecal reservoir); Ind, induction; isp, intraspinal (via lumbar spinal tap); y, years; cons, consolidation; med age, median age; med. OS, median overall survival; Med. PFS, median progression-free survival; N, sample size; NS, not stated; NT, delayed neurotoxicity; ORR, overall response; PR, partial remission; R, rituximab; RT, radiotherapy; TM, treatment-associated mortality; TMZ, temozolomide; TT, thiotepa; TTP, time to progression

*¹ Follow-up publication with long-term data

*² 1. randomization

*³ 2. randomization

combination with rituximab (e24), the PCV regimen (procarbazine, CCNU, and vincristine) (e25), and rituximab and ifosfamide plus etoposide (e26). With response rates of 74% to 79% and a median survival of 10 to 16 months, whole-brain radiotherapy for recurrence is an effective treatment option (e27, e28). However, it should be used late in the course of the disease, if possible, as it is associated with a high rate of severe neurotoxic adverse events among patients with prior intensive chemotherapy (e28).

New active substances and immunotherapies

In refractory patients with multiple previous therapies, substances, such as temsirolimus (e29), lenalidomide (e30) and ibrutinib (e31), which interfere with B-cell receptor signaling and thus have an effect on proliferation and survival of lymphoma cells, and so-called checkpoint inhibitors (e32), which modulate T cell-mediated immune response, show activity, but are associated with significant toxicity in some patients. Should their efficacy and tolerability be confirmed in the currently recruiting studies, new treatment options for patients with PCNSL may become available.

Special patient populations

Management of older patients

The treatment of elderly patients is limited by comorbidities and the increased risk of treatment-related side effects. HD-MTX-based polychemotherapy is safe and effective as long as renal function is taken into account (dose reduction if creatinine clearance <100 mL/min) (29). Complete remissions are achieved in 36% to 60% of patients; however, median overall survival is only 14 to 31 months (e6, e33, e34) (Table). In the German-speaking countries, many centers have adopted the PRIMAIN protocol (rituximab, methotrexate, procarbazine, [eTable 2]) which was evaluated in a large, randomized, multicenter study (e33).

If HD-MTX is contraindicated, patients can be treated with temozolomide for which an overall response of 47% and overall survival of 21 months was found in a retrospective analysis (e35). Given the high risk of neurotoxic adverse events, whole-brain radiotherapy should only be used if other treatment alternatives are not available or have been exhausted (2).

See the *eSupplement* for the sections “Management of vitreoretinal lymphoma” and “Management of immunocompromised patients”.

Follow-up care

The follow-up should be based on neurological examination and cranial magnetic resonance imaging; other investigations are only recommended if specific abnormalities are suspected. The requirements for complete remission include the complete disappearance of contrast-enhancing lesions, the absence of malignant cells in the cerebrospinal fluid, and the complete disappearance of previous ocular involvement. All patients should undergo imaging and clinical follow-up

KEY MESSAGES

- Clinical and imaging findings can be nonspecific—consequently, PCNSL should always be included in the differential diagnosis of space-occupying lesions of the brain and steroid treatment should be avoided prior to histopathological confirmation of the diagnosis to improve the diagnostic sensitivity of the biopsy.
- The first-line treatment for PCNSL is HD-MTX-based polychemotherapy; treatment protocols commonly used for the various age groups in the German-speaking countries (Bonn protocol, Freiburg protocol, Matrix protocol, Primain protocol) are listed in the *eSupplement*.
- Radiotherapy should be avoided in the first-line treatment of PCNSL and be reserved for patients with relapse or those with contraindications to chemotherapy.
- Given the very high toxic potential of the therapies for PCNSL, patients should preferably be treated in a center experienced in the management of the disease.
- In general, it is recommended that treatment decisions be made by multidisciplinary teams, e.g. dedicated brain tumor or lymphoma boards.

examinations at 3-month intervals for 2 years, then at 6-month intervals for 3 years and finally at 1-year intervals for 5 years (2). Additional checks should be performed to assess any suspected abnormalities. With regard to potential neurotoxic late complications, it is advisable that patients receive follow-up care in a neuro-oncological center.

Conclusion

Because of its specific biological and clinical features, the diagnosis and treatment of PCNSL is challenging and requires an interdisciplinary approach. Thus, it is crucial that patients are preferably treated in centers experienced in the management of the disease and in the setting of a clinical study.

Conflict of interest statement

Prof. Illerhaus has received consultancy fees from Riemser. He has received fees for conference participation and reimbursement of travel and accommodation expenses from Riemser and Roche. He has been contracted and received fees for the conduction of clinical trials from Riemser.

Dr. Korfel has received consultancy fees and fees for preparing continuing medical education events from PIQUR, Mundipharma, and Riemser.

Prof. Schlegel has received lecture fees for Neuro-update from medupdate.

Prof. Dreyling has received consultancy fees from Bayer, Celgene, Gilead, Janssen, Mundipharma, Roche, and Sandoz. He has received fees for preparing continuing medical education events from Bayer, Celgene, Gilead, Janssen, and Roche. He has received financial support from Celgene, Janssen, Mundipharma, and Roche for a research project that he initiated.

Dr. von Baumgarten and Prof. Deckert declare that no conflict of interest exists.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref2518

eSupplement, eTables:

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Supplementary material to:

The Diagnosis and Treatment of Primary CNS Lymphoma

An Interdisciplinary Challenge

by Louisa von Baumgarten, Gerald Illerhaus, Agnieszka Korfel, Uwe Schlegel, Martina Deckert, and Martin Dreyling

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eSUPPLEMENT

• The management of vitreoretinal lymphoma

Almost all patients with isolated vitreoretinal lymphoma develop a CNS manifestation over the course of the disease (e36). Whether its management should be based on local strategies alone (ocular radiation therapy, intravitreal MTX-/rituximab injections) or on systemic approaches analog to the treatment of PCNSL, remains the subject of controversy (e36). In two retrospective case series, systemic therapy provided no survival benefit compared to local treatment alone (e37, e38); thus, it may be justified to delay the initiation of systemic therapy until the occurrence of a CNS manifestation.

If patients present with both ocular and CNS involvement, treatment as in patients with CNS involvement alone is recommended, because local treatment in addition to systemic therapy does not appear to improve survival (e39).

• Management of immunosuppressed patients

The data available on the management of PCNSL in immunocompromised patients is limited to small case series. Patients with HIV-associated PCNSL benefit from highly active anti-retroviral therapy (HAART) (e40). In patients after organ transplantation, immunosuppressive therapy should be reduced or modified. If possible, immunosuppressed PCNSL patients should receive the same therapy as immunocompetent patients (e41). A single-center case series showed that selected patients may also be eligible for HD-MTX/rituximab treatment with subsequent HD-ASCT (e42).

• Interdisciplinary networking

The CNS lymphoma study group of the German Competence Network Malignant Lymphoma (Kompetenznetzes für maligne Lymphome, KML), the CNS-NHL study group of the German Lymphoma Alliance (GLA), and the interdisciplinary consortium Network Lymphomas and Lymphomatoid Lesions in the Nervous System (Netzwerk Lymphome und lymphomatoide Läsionen des Nervensystems, NLLLN) (e45) are important integrated platforms for sharing clinical and scientific information and for coordinating clinical studies. In addition, the NLLLN offers consultancy services (second opinions) and support in the management of complex cases. The guidelines on the diagnosis and treatment of PCNSL were published with contributions from the authors (see e46) and are currently being revised.

eTABLE 1

Studies currently recruiting in Germany

MATRIX	Multicenter phase III trial on high-dose chemotherapy and autologous stem cell transplantation compared with conventional chemotherapy for consolidation in primary CNS lymphoma Age: 18–65 years (65–70 years only if ECOG status 0–1)
MARTA	Multicenter phase II study on age-adapted high-dose therapy followed by autologous stem cell transplantation in fit older patients with newly diagnosed primary CNS lymphoma Age: >70 years, ECOG status ≤ 2 (65–70 if patients are not eligible for MATRIX))
PQR309	Open, non-randomized phase II study to evaluate the efficacy and safety of pan-PI3K and mTOR PQR309 in patients with relapsed or refractory primary CNS lymphoma Age ≥18 years, Karnofsky index (KPS) ≥70%
NOA-13	Prospective observational study on chemotherapy in non-specifically pre-treated patients with primary CNS lymphoma (PCNSL)

ECOG, Eastern Cooperative Oncology Group status; CNS, central nervous system

eTABLE 2

Common treatment protocols with dosages
MATRIX patients up to age 65 years (65–70 years only in ECOG 0–1)
Induction therapy

Rituximab	375	mg/m ²	i. v.* ¹	days –5, 0
Methotrexate* ²	3.5	g/m ²	i. v. (3 h 15')* ³	day 1
Cytarabine* ⁴	2 × 2	g/m ²	i. v. (1 h)	days 2, 3
Thiotepa	30	mg/m ²	i. v. (1 h)	day 4

4 cycles, repeat every 3 weeks

HD-ASCT protocol

Rituximab	375	mg/m ²	i. v.* ¹	day –7
BCNU	400	mg/m ²	i. v. (1 h)	day –6
Thiotepa	2 × 5	mg/kg	i. v. (2 h)	days –5, –4
ASCT				day 0

Non-myeloablative consolidation (R-DeVic)

Rituximab	375	mg/m ²	i. v.* ¹	day 0
Dexamethasone	40	mg	i. v.	days 1–3
Etoposide (VP-16)	100	mg/m ²	i. v. (2 h)	days 1–3
Ifosfamide	1500	mg/m ²	i. v. (2 h)	days 1–3
Carboplatin	300	mg/m ²	i. v. (1 h)	day 1

2 cycles, repeat every 3 weeks

Freiburg ZNS-NHL protocol—for patients with primary non-Hodgkin lymphomas of the CNS up to age 65 years (potentially 65–70 years, but only if ECOG 0–1 and excellent general condition)
Induction therapy

Rituximab	375	mg/m ²	i. v.* ¹	days 0,10
Methotrexate* ²	8	g/m ²	i. v. (4 h)	days 1,11

2 cycles, repeat on day 20

Cytarabine* ³	3	g/m ²	i. v. (3 h)	days 2, 3
Thiotepa	40	mg/m ²	i. v. (1 h)	day 4

1–2 cycles, depending on response; repeat on day 21

HD-ASCT protocol

BCNU	400	mg/m ²	i. v. (1 h)	day –6
Thiotepa	2 × 5	mg/kg	i. v. (2 h)	days –5, –4
ASCT				day 0

Bonn protocol—for patients up to age 75 years

Cycle A

Methotrexate* ²	5	g/m ²	i. v. (24 h)* ⁵	day 1
Vincristine	2	mg	i. v. (15 min)	day 1
Ifosfamide	800	mg/m ²	i. v. (1 h)	days 2–5
Dexamethasone	10	mg/m ²	p. o.	days 2–5
Prednisolone	2,5	mg	i. c. v.	days 1–4
Methotrexate	3	mg	i. c. v.	days 1–4
Cytarabine	30	mg	i. c. v.	day 5

Cycle B

Methotrexate* ²	5	g/m ²	i. v. (24 h)* ⁵	day 1
Vincristine	2	mg	i. v. (15 min)	day 1
Cyclophosphamide	200	mg/m ²	i. v. (1 h)	days 2–5
Dexamethasone	10	mg/m ²	p. o.	days 2–5
Prednisolone	2,5	mg	i. c. v.	days 1–4
Methotrexate	3	mg	i. c. v.	days 1–4
Cytarabine	30	mg	i. c. v.	day 5

Cycle C

Cytarabine	3	g/m ²	i. v. (3 h)	days 1, 2
Vindesine	5	mg	i. v. (15 min)	day 1
Dexamethasone	20	mg/m ²	p. o.	days 2–5
Prednisolone	2,5	mg	i. c. v.	days 1–4
Methotrexate	3	mg	i. c. v.	days 1–4
Cytarabine	30	mg	i. c. v.	day 5

6 cycles, repeat day 14, cycle sequence: A1, B1, C1, A2, B2, C2

PRIMAIN protocol for older or fragile patients

Induction therapy:

Rituximab	375	mg/m ²	Inf.* ⁴	days 1, 15, 29
Methotrexate* ²	3,0	g/m ²	Inf. (4 h)	days 2, 16, 30
Procarbazine	60	mg/m ²	p. o.	days 1–10

6 cycles, repeat day 28

Maintenance therapy:

Procarbazine	100	mg/m ²	p. o.	days 1–5
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6 cycles, repeat day 28

*¹ Rituximab: Rituximab: protracted infusion on initial administration 1st hour 50 mg/h, 2nd hour 100 g/h and 3rd hour 150–250 mg/h

*² HD-MTX: This treatment requires regular measuring of MTX levels and leucovorin rescue as well as a corresponding adjunctive therapy and emergency treatment

*³ 0.5 g/m² in 15 min + 3 g/m² over 3 h

*⁴ Conjunctivitis prophylaxis: steroid-containing eye drops

*⁵ 0.5 g/m² in 30 min. + 4.5 g/m² over 23.5 h

ECOG, Eastern Cooperative Oncology Group status; HD-ASCT, high-dose chemotherapy with subsequent autologous stem cell transplantation; HD-MTX, high-dose methotrexate; i.c.v.= administration via an intrathecal reservoir; i.v., intravenous; p. o., per os