VIA MEDICA

REVIEW ARTICLE

Michał Osowiecki, Beata Ostrowska, Jan Walewski

Klinika Nowotworów Układu Chłonnego, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie w Warszawie

Primary central nervous system lymphoma — a review of current therapeutic strategies

Address for correspondence:
Lek. Michał Osowiecki
Klinika Nowotworów Układu Chłonnego
Centrum Onkologii — Instytut
im. Marii Skłodowskiej-Curie
ul. Roentgena 5, 02–781 Warszawa
e-mail: mosowiecki@coi.pl

Oncology in Clinical Practice
2015, Vol. 11, No. 6, 310–316
Translation: Piotr Hołownia, PhD

ISSN 2450–1654
www.opk.viamedica.pl

ABSTRACT

Primary central nervous system lymphoma (PCNSL) is a highly aggressive extranodal lymphoma subtype arising in the brain parenchyma, spinal cord, meninges, cranial nerves, and/or intraocularly. PCNSL accounts for 3% of brain tumours and 2–3% cases of non-Hodgkin's lymphoma. Diffuse large B-cell lymphoma (DLBCL) is a primary diagnosis in 95% of all PCNSL, with highly aggressive lymphomas (Burkitt's lymphoma, lymphoblastic lymphoma) and marginal zone lymphoma (MZL) or T-cell lymphomas accounting for the other 5%. Over the last 40 years, PCNSL rates have been increasing. Although PCNSL shares many histopathological features with DLBCL (not otherwise specified; NOS), its prognosis is generally far worse. The current WHO 2008 classification for cancers of the haematopoietic system and lymphomas assigns DLBCL CNS into a distinct diagnostic entity of lymphoma.
Key words: lymphoma, central nervous system, methotrexate

Oncol Clin Pract 2015; 11, 6: 310–316

Aetiology and pathogenesis

Primary central nervous system lymphoma (PCNSL) accounts for 2–3% cases of non-Hodgkin's lymphoma. Diffuse large B-cell lymphoma (DLBCL) is a primary diagnosis in 95% of all PCNSL [1]. Incidence of PCNSL in continuously increasing [2]. The aetiology is not yet fully known. The most significant risk factors are immune-deficiencies that can be congenital (e.g. Wiskott-Aldrich syndrome) or acquired (e.g. AIDS). Indeed, PCNSL is AIDS-defining condition and as such it demonstrates 100% correlation with Epstein-Barr virus (EBV) infection. Another high-risk group includes post-organ transplant patients. The risk of post-transplant lymphoproliferative disorders (PTLD) with central nervous system (CNS) involvement ranges from 2 to 7% in those after heart, lung, and liver transplant and from 1 to 2% after kidney transplant [3]. Primary central nervous system lymphoma falls within the DLBCL subtype of activated B-cells after leaving germinal centres (i.e. activated B-cell like, ABC DLBCL), which express about 95% MUM1, 50–80% BCL-6+, and about 10% CD10+ [4]. Molecular analysis is very difficult because of the dearth of biopsy material usually found. The most frequent chromosome aberrations (56–79%) are deletion of part of chromosome 6p21-6p25 that includes the HLA locus (linked to chemotherapy resistance) and silencing of the expression of the cell cycle regulator *CDKN2A*. The aberrant activation of the NF$\kappa\beta$ complex is also characteristic with resulting increased copies of the *MALT1* gene and mutations activating *CARD11* and *MyD88* [5].

Several such pathogenic sites may potentially provide molecular targets for drugs like ibrutinib, fostamatinib (B-cell receptor), ruxolitinib (JAK/STAT site), lenalidomide, pomalidomide (IRF4/MYC), and inhibitory MALT1 (via the NFκB complex). Because of molecular differences, a worse prognosis, and the need to adopt specific therapeutic regimens, the WHO classifies DLBCL CNS as a distinct lymphoma disease entity [6].

Clinical symptoms

Median age at patient diagnosis is 56 years (45–70), with males being slightly more common. Half of suffer-

ers show behavioural disturbances and focal neurologic symptoms characteristic of tumour localisation and infiltrated structures of the CNS (paresis, along with impairment of the senses, speech, sight, hearing, and others). In 35% of cases, signs of intracranial pressure are observed whilst in 15% and 4% of cases, respectively, seizures and visual impairment are reported [7]. In 70% cases, neuroimaging techniques demonstrate singular lesions (in AIDS patients lesions are more often multiple ones), where they usually appear in both cerebral hemispheres. Between 15 and 20% of lesions are involved with the meninges, and intraocular presentation occurs in 10–20% of cases. Systemic symptoms, however, appear sporadically.

Diagnosis

Clinical symptoms are non-specific. The basic diagnostic technique for patients with suspected brain tumour is magnetic resonance (MR) using gadolinium for contrast enhancement. Over 95% of cases of PCNSL demonstrate a uniformly typical reinforcement around the tumour site. Glioblastoma can be suspected if necrosis has occurred. As mentioned previously, the majority of PCNSL tumours occurring in immuno-competent patients are solitary, whilst those in AIDS patients are frequently multifocal. Even for radiological changes that constitute typical PCNSL features, a stereotactic biopsy is required in order to confirm diagnosis. Glucocorticosteroids (GS) use may pose great difficulties for making diagnoses, in that the resulting spectacular remissions make biopsies challenging. This can lead to considerable delays in diagnosis, lasting weeks and even months [8]. It is therefore recommended that GSs are withheld 7–10 days prior to the planned biopsy. In the absence of any contra-indications, complete or partial tumour resection is equally admissible.

For performing cytological and biochemical measurements of cerebrospinal fluid (CSF) infiltration, lumbar puncture is used for obtaining such samples. Flow cytometry of CSF is performed due its greater sensitivity and specificity [9, 10]. Indeed, a future and universal method for making an effective diagnosis would be for detecting micro-RNA (miRNA) in CSF. This is a short and non-coding RNA fragment the over-expression of which is linked to the presence of many cancers. The *miR-21*, *miR-19b*, and *miR92a* subtypes found in CSF are characteristic markers of PCNSL as determined by the real-time polymerase chain reaction (qRT-PCR). A 95% level of sensitivity and specificity has been achieved when measuring the presence of miRNA as a marker for diagnosing PCNSL [11]. In 4–12% of patients suspected of PCNSL, the disease can spread beyond the CNS, thereby necessitating whole body CT scans [12]. In accordance to the new Lugano classification, FDG-PET-CT [13] is a very sensitive technique. Further diagnostic tests include neurological and ophthalmic (using slit lamps) ones as well as blood tests (LDH measurement and virological testing) and ultrasound of the testis. For PCNSL, infiltration of the bone marrow occurs in around 1% of cases so that biopsy becomes unnecessary, especially if the PET-CT results prove negative.

Prognostic determinants/factors

The International Prognostic Index (IPI) for aggressive lymphomas has no direct bearing on the prognosis of PCNSL. Based on a retrospective study of 378 PCNSL patients at 23 medical centres, the International Extranodal Lymphoma Study Group (IELSG) has developed a prognostic system depending on evaluating five variables that have been associated with an unfavourable prognosis, namely: > 60 years of age, Eastern Cooperative Oncology Group (ECOG) score > 1, LDH concentrations > N, raised CSF protein levels, and infiltration of deep brain structures (i.e. periventricular areas, basal ganglia, brain stem, and cerebellum). In patients with 0–1, 2–3, or 4–5 of these factors the overall survival (OS) after two years is, respectively, 80%, 48%, and 15% [14]. However, currently this model is rarely used because new treatments have become more effective, thereby making the value of such prognostic traits less significant (e.g. disease localisation and levels of blood LDH and CSF protein). A different but universally used system is the 'Memorial Sloan Kettering Cancer Centre Prognostic Model' from the USA, which is based on a retrospective study on 338 patients with PCNSL in which highly significant prognostic determinants were found to be age (≤ 50 vs. > 50 years) and the Karnofsky Performance Score (KPS); ≥ 70% vs. < 70%. Based on these two criteria, three risk groups were identified; low (age ≤ 50 years), medium (age > 50 years, KPS ≥ 70%), and high (age > 50 years, KPS < 70%), for which the median OS were, respectively, 5.2, 2.1, and 0.8 years [15].

Treatment

Radiotherapy

Historically speaking, whole brain radiotherapy (WBRT) has been the primary method for treating PCNSL. By such means, very effective remissions were achieved; however, median OS rates were very short at around 12 months [16, 17]. High rates of local recurrence, the lack of controlling the disease spread outside the radiation field, together with the radiotherapy being

highly neurotoxic has driven the search for alternative treatments [7, 18]. Even in the 1970s, methotrexate therapy (MTX) had been shown to be highly effective for PCNSL [19] where a study by DeAngelis et al. treated 31 PNSCL patients by combined regimens of intravenous MTX (1 g/m^2) and intraventricular MTX followed by WBRT and then by high doses of cytosine arabinoside (Ara-C), whereas WBRT as a monotherapy was given to 16 patients. The median OS in the combination-treated patients was 42.5 months, whilst that for the monotherapy was 21.7 months [20]. This result served to prompt the use of multi-drug regimens complementary to WBRT.

A big therapeutic problem is the neurotoxicity of radiotherapy when used alone or in combination. WBRT adversely affects brain cognition, particularly in the elderly (> 60 years old). Other adverse features are urinary incontinence and abnormal gait and speech. Such impairments lead to the patient losing their independence [21]. When considering ways to lengthen the patient's survival time, a treatment regimen is sought that will maximise the therapeutic benefits without the adverse effects of WBRT on the functioning of the patient. In those patients without WBRT treatment, 12 years of post-treatment observation has demonstrated their cognitive behaviour to be adequate in most cases [22]. One way of reducing the neurotoxic risk is through reducing the WBRT dose to 23.4 Gy (rWBRT, reduced WBRT), as shown in the study by Shah et al. After achieving CR post treatment with rituximab, MTX, procarbazine, and vincristine followed by rWBRT consolidation, a 67% rate of two-year survival was seen in the absence of any neurotoxic events [23]. A study by Korfel et al. demonstrated that omitting WBRT in standard doses (as adjuvant therapy post-induction MTX-based chemotherapy) has no effect on the OS [24]. Likewise, a study by Thiel et al. showed no gains in OS when adopting complementary WBRT [25]. It should be noted that for elderly patients aged > 60 years, giving complementary WBRT in reduced doses results in poorer progression-free survival (PFS) compared to younger patients; the 3-year PFS being 88% vs. 53% in patients over 60 years old. Furthermore, in this study by Morris et al., it should be stressed that the three-year OS was 87% in those post-R-MPV treatment (rituximab, MTX, procarbazine, vincristine) followed by rWBRT with minimal neurotoxicity [26].

Surgical treatment

As previously stated, stereotactic biopsy is the preferred material used for diagnostic testing. Until recently, practically all recommendations have strongly advised against tumour resection, which has a insignificant effect on OS, but potentially increases the risk of neurological deficit during the PCNSL post-operative phase [27]. Nonetheless, a prospective PCNSL German study (SG-1) has shown improved PFS in patients after tumour resection [28]. Our own observations have additionally confirmed improvements in PFS when lesions in the CNS have been resected [29]. Based on the authors' opinions, it is suggested that tumour resection, when performed within patient safety limits or by using modern neurological mapping techniques, is of therapeutic benefit without harming the patient's neurological functioning.

Chemotherapy

Methotrexate forms the basis of all multi-drug regimens for treating PCNSL [18, 30]. Patients in a favourable clinical condition receive MTX doses of ≥ 3.5 g/m^2. It seems that giving such high intravenous MTX (HD-MTX) doses eliminates the need for additional intrathecal treatment [31]. A prospective Phase II study by Batchelor et al., conducted under the auspices of 'The New Approaches to Brain Tumour Therapy (NABTT — CNS)' consortium, demonstrated that using MTX (8 g/m^2) every two or four weeks results in a complete remission (CR) incidence of 52%; the median PFS was 12.8 months and the OS was 55.4 months [32]. A study by DeAnglis et al. from 2002 used five cycles of MTX on 98 subjects at a dose of 2.5 g/m^2 vincristine, procarbazine, along with intrathecal MTX at 12 mg, carried out complementary to WBRT, after which all patients received a high dose Ara-C as consolidation. A high objective response rate (ORR) of 94% was observed, with a median PFS of 24 months and median OS of 36.9 months [33]. Based on the promising findings of the DeAnglis et al. study, further studies were aimed to determine the efficacy of other multi-drug regimens. As a result the efficacy of various drugs penetrating the CNS were established (thiotepa, busulfan, etoposide, carmustine, and others) [34, 35]. A randomised IELSG study by Ferreri et al. on 79 patients treated with high-dose MTX and Ara-C followed by WBRT showed a gain of eight months of failure free survival (FFS) compared to a FFS of four months in patients not receiving Ara-C. In combination therapy, radiological CR outcomes (46% in the MTX/araC arm vs. 18% in the MTX arm), along with improved OS trends in the combination arm have been recognised as effective means of treating PCNSL [36]. The CALGB 50202 study demonstrated the effectiveness of giving MTX, temozolamide, rituximab, and consolidation with Ara-C and etoposide (EA). This two-stage treatment aims to provide a number of effective drugs without causing any significant myelosuppression that delays the first and most important phase of the therapy. The median time to progression (TTP) is four years, while the median OS was not attained after and over five years of observation [37].

The aforementioned toxicity of WBRT inclines towards searching for alternative methods for consolidating the achieved remission through use of induction chemotherapy based on high-dose MTX. Attempts at consolidation have been made by using myeloablative chemotherapy and autologous hematopoietic stem cell transplantation (auto-HCT). A French study, GOELAMS, (i.e. *Groupe Ouest-Est d'Etude des Leucémies Aigues et autres Maladies du Sang)*, on 25 patients aged below 60 years, obtained an OS of 64% and event free survival (EFS) of 46% when adopting a regimen of a MTX program/etoposide/carmustine/ifosphamide/cytarabine with auto-HCT consolidation after four years of follow-up [38]. A study by Chen et al. on 30 lymphoma patients (both primary and secondary CNS) adopted the TBC regimen (thiotepa, busulfan, cyclophosphamide) and auto-HCT with high doses of rituximab (1000 mg/m^2). In those with PCNSL (n = 18), there was no recurrence after two years of observation. The OS for all 30 subjects (including 12 with secondary CNS involvement), achieved an OS of 93% after two years [39]. Similar outcomes were obtained in a phase II study on PCNSL patients after treatment with R-MPV (rituximab, MTX, procarbazine, vincristine). Patients achieving complete or partial remission were given the TBC consolidation and auto-HCT. After 45 months of observation, neither a median PFS or OS had been attained. A two-year OS was observed in 81% of those that underwent auto-HCT [40]. Indeed, the aim of a multi-centre Alliance 51101 study currently being undertaken in the USA is to compare the efficacy of intensified treatment (EA — etoposide, Ara-C) with myeloablative therapy (carmustine, thiotepa, auto-HCT) (NCT01511562). There are also two other pending studies, in the recruitment phase, by the IELSG group, whose aim is to determine the efficacy of auto-HCT when used as a first-line treatment for PCNSL patients (NCT01011920, NCT02329080). One of these (IELSG 32) has already demonstrated improvement in the two-year OS and FFS (respectively, 66 ± 6% and 64 ± 6%) after the first observation period was closed in patients with combined MTX and Ara-C, in whom rituximab and thiotepa (MATRIX) had been adopted. In the MTX/Ara-C arm and rituximab/MTX/Ara-C arm, the OS was, respectively, 40 ± 6% and 58 ± 6% [41]. In this same study a second randomisation is in progress the aim of which is to determine the efficacy of WBRT and auto-HCT consolidation in patients objectively responding to induction therapy. The advantages of using auto-HCT in first-line treatment has been shown in a retrospective analysis of 105 PCNSL patients who had undergone auto-HCT consolidation between 1997 and 2011; the median PFS and OS being, respectively, 85 and 121 months whereas the OS rate after 2 and 5 years was, respectively, 82% and 79% [42]. Table 1 presents the results of the most important studies published recently.

Rituximab

Rituximab is an anti-CD20 monoclonal antibody used as a standard treatment for DLBCL lymphoma at extra-CNS sites. Being such a large molecule, it is considered that rituximab is unable to appreciably cross

Table 1. Selected treatment regimens for primary central nervous system lymphoma (PCNSL)

Study	N	Drugs	Response rates (%)	PFS (%)	OS (%)
Ferreri 2009 [36]	39	MTX 3.5 g/m^2, Ara-C, WBRT	69%	FFS 38% 3 years	46% 3 years
Shah 2007 [23]	30	R-MPV (MTX 3.5 g/m^2), Ara-C, WBRT	93%	57% 2 years	67% 2 years
Thiel 2010 [25]	318	MTX 4 g/m^2 ± WBRT	WBRT: CR 36%, without WBRT: CR 58%	18.3 med. 11.9 med. (months)	32.4 med. 37.1 med. (months)
Rubenstein 2013 [37]	44	MTX 8 g/m^2 , TMZ, R, E, Ara-C	77%	57% 2 years	65% 4 years (unattained)
Morris 2013 [26]	52	MTX 3.5 g/m^2, R, VCR, PCB, Ara-C, WBRT	95%	77% 2 years	80% 5 years
Omuro 2015 [40]	32	MTX 3.5 g/m^2, R, PCB, VCR, auto-HCT	97%	81% 5 years	81% 5 years
Chen 2015 [39]	30	R, TT, B, CTX, auto-HCT	Not	81% 2 years	93% 2 years
Ferreri 2015 [41]	227	MATRIX (MTX 3.5 g/m^2)	87%	FFS 64 ± 6%, 2 years	66 ± 6% 2 years

Ara-C — cytosine arabinoside; auto-HCT — autologous haematopoietic cell transplantation; B — busulfan; CTX — cyclophosphamide; E — etoposide; FFS — time off from failures; MATRIX — methotrexate, cytosine arabinoside, thiotepa, rituximab; med — median; MTX — methotrexate; PCBs — procarbazine; R — rituximab; R MPV — rituximab, methotrexate, procarbazine, vincristine; TMZ — temozolomide; TT — thiotepa; VCR — vincristine; WBRT — whole brain radiotherapy

the blood brain barrier (BBB); following intravenous injection, concentrations of this antibody are 0.1–4.4% of those measured in the blood. Nevertheless, radiological and clinical responses (by MR imaging) are observed after rituximab monotherapy [43]. Furthermore, the efficacy of rituximab was demonstrated in conjunction with CHOP chemotherapy by reduced DLBCL relapses in the CNS compared to using CHOP alone [44]. A retrospective study by Holdoff et al. confirmed the advantages of using rituximab combined with chemotherapy. In patients receiving HD-MTX, the median OS was 16.3 months, whilst in the group where rituximab was also administered this median OS had not been reached; the median PFS, respectively, being 4.5 months and 26.7 months [45]. There are also reports on the efficacy of rituximab when given intrathecally or intraventricularly [46]. Rituximab is currently recommended for treating PCNSL in conjunction with chemotherapy. It is suggested that rituximab is given at increased doses during the first weeks of treatment when the BBB becomes damaged in areas occupied by actively changing tumours. The frequent administration of standard or raised rituximab doses every 7–14 days (500–1000 mg/m^2) aims to exploit the BBB leaks during the initial phase of therapy and thereby increase the penetration of rituximab into the CNS, thus maximising the therapeutic effects during the first 7–8 weeks of treatment. After this time, when the tumour has usually completely or partially regressed, the integrity of the BBB becomes restored.

Treating recurrence

Irrespective of the first-line therapy, disease recurrence or resistance to induction treatment occurs in a significant group of PCNSL patients. An optimal strategy for dealing with this situation has not yet been established. Repeated treatment with HD-MTX has been attempted in those in at least 12 months remission [47]. Patients not previously treated with radiotherapy may benefit from WBRT [48]. A study by Soussain et al. showed that patients with refractory or relapsed PCNSL received Ara-C and etoposide along with consolidation using high doses of thiotepa, busulfan, and cyclophosphamide followed by auto-HCT. The median OS for those given auto-HCT was 58.6 months [49]. These results are consistent with more recent findings from this group in a 79-patient subject group, where the five-year OS rate was 51% after administering the same consolidation regimen, as well as 62% of patients preserving their susceptibility to chemotherapy [50]. The results of a Berlin group study on relapsed patients demonstrated a two-year TTF rate of 49% in all subjects and a 58% rate in those post-auto-HCT; chemotherapy consisting of HD-MTX that included cytarabine, thiotepa, ifosphamide, and intrathecal administration of liposomal cytarabine, followed by myeloablative chemotherapy (thiotepa, etoposide, carmustine) and then auto-HCT [51]. Preliminary findings of a German prospective study, (presented at the 56th congress of the American Society of Haematology (ASH) in 2014), showed that the 'intent-to-treat group' (n = 38) of patients with relapsed or refractory PCNSL treated by auto-HCT achieved a 57.9% OS rate and a 13.2% partial remission (PR). In the group that completed the treatment (n = 31), the annual and two yearly OS rate was, respectively, 63% and 57% [52].

Summary

PCNSL is a subtype of DLBCL, which is distinguished not only by its specific location, but through its immuno-phenotypic and molecular features. Such features correspond to the activated B-cell-like (ABC) post-germinal cells in which activation occurs of the BCR signalling receptor and NFκB complex, as well as the JAK/STAT pathway following IL-10 receptor activation. The biological characteristics of PCNSL together with its localisation protected by the BBB make conventional immune-chemotherapy fail, which is highly effective in nodal DLBCL. The basis of PCNSL treatment is multi-drug chemotherapy consisting of MTX in doses of $\geq$ 3.5 g/m^2, an alkylating agent, and rituximab, which should be given in the shortest time intervals to obtain an optimal response. In consolidating remission, cytosine arabinoside is used in high doses and etoposide. If the patient is in a favourable medical condition, then myeloablative chemotherapy is adopted by using drugs that cross the BBB, such as thiotepa, busulfan, and cyclophosphamide, followed by auto-HCT. Historically, WBRT was a commonly used method for consolidation, but due to the high incidence of encephalopathy post-irradiation and the previous exposure to high doses of MTX, randomised studies have been undertaken to confirm the value of this treatment, particularly exploring reduced radiation doses. For many patients, however, chemotherapy together with high MTX doses and auto-HCT consolidation cannot be used because of advanced age and poor health. For such reasons, studies are being performed on drugs that selectively act on signalling pathways that become pathologically active, this being expected to give potent clinical responses coupled with low toxicity [53].

References

1. Batchelor T, Loeffler J. Primary CNS lymphoma. J Clin Oncol 2006; 24: 1281–1288.
2. Olson J, Janney A, Rao R et al. The continuing Increase in the Incidence of primary central nervous system non-hodgkin lymphoma. A surve-

illance, epidemiology, and end results analysis. Cancer 2002; 95: 1504–1510.
3. Schabet M. Epidemiology of primary CNS lymphoma. J Neurooncol 1999; 43: 199–201.
4. Camilleri-Broët S. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. Blood 2006; 107: 190–196.
5. Ponzoni M, Issa S, Batchelor T, Rubenstein JL. Beyond high-dose methotrexate and brain radiotherapy: novel targets and agents for primary CNS lymphoma. Ann Oncol 2014; 25: 316–322.
6. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011; 117: 5019–5032.
7. Rubenstein JL, Gupta NK, Mannis GN, LaMarre AK, Treseler P. How I treat CNS lymphomas. Blood 2013; 122: 2318–2330.
8. Pirotte B, Levivier M, Goldman S, Brucher JM, Brotchi J, Hildebrand J. Glucocorticoid-induced long-term remission in primary cerebral lymphoma: case report and review of the literature. J Neurooncol 1997; 32: 63–69.
9. Benevolo G, Stacchini A, Spina M et al. Final results of a multicenter trial addressing role of CSF flow cytometric analysis in NHL patients at high risk for CNS dissemination. Blood 2012; 120: 3222–3228.
10. Hegde U, Filie A, Little RF et al. High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk for central nervous system involvement: the role of flow cytometry versus cytology. Blood 2005; 105: 496–502.
11. Baraniskin A, Kuhnhenn J, Schlegel U et al. Identification of microRNAs in the cerebrospinal fluid as marker for primary diffuse large B-cell lymphoma of the central nervous system. Blood 2011; 117: 3140–3146.
12. Abrey LE, Batchelor TT, Ferreri AJM et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005; 23: 5034–5043.
13. Cheson B, Fisher R, Barrington S et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma — the Lugano Classification. J Clin Oncol 2014; 32: 3059–3067.
14. Ferreri AJM, Blay JM, Reni M et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol 2003; 21: 266–272.
15. Abrey LE, Ben-Porat L, Panageas KS et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol 2006; 24: 5711–5715.
16. Henry JM, Heffner MM, Dillard SH, Earle KM, Davis RL. Primary malignant lymphomas of the central nervous system. Cancer 1974; 34:1293–1302.
17. Nelson DF, Martz KL, Bonner H et al. Non- Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 1992; 23: 9–17.
18. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol 1998; 16: 859–863.
19. Ervin T, Canellos GP. Successful treatment of recurrent primary central nervous system lymphoma with high-dose methotrexate. Cancer 1980; 45: 1556–1557.
20. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. J Clin Oncol 1992; 10: 635–643.
21. DeAngelis LM. Primary CNS lymphoma: treatment with combined chemotherapy and radiotherapy. J Neurooncol 1999; 43: 249–257.
22. Doolittle ND, Dósa E, Fu R et al. Preservation of cognitive function in primary CNS lymphoma survivors a median of 12 years after enhanced chemotherapy delivery. J Clin Oncol 2013; 31: 4026–4027.
23. Shah GD, Yahalom J, Correa DD et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. J Clin Oncol 2007; 25: 4730–4735.
24. Korfel A, Thiel E, Martus P et al. Randomized phase III study of whole--brain radiotherapy for primary CNS lymphoma. Neurology 2015; 84: 1242–1248.
25. Thiel E, Korfel A, Martus P et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol 2010; 11: 1036–1047.
26. Morris PG, Correa DC, Yahalom J et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radio- therapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long- term outcome. J Clin Oncol 2013; 31: 3971–3979.
27. Bataille B, Delwail V, Menet E et al. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg 2000; 92: 261–266.
28. Weller M, Martus P, Roth P, Thiel E, Korfel A. Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro Oncol 2012; 14: 1481–1484.
29. Ostrowska B, Osowiecki M, Domanska-Czyz K et al. CHOP-R and high-dose methotrexete in the primary CNS lymphoma revisited: 10-year experience and 92 patients from single institution. Blood 2013; 122: 3051.
30. Blay JY, Conroy J, Chevreau C et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 1998; 16: 864–871.
31. Khan RB, Shi W, Thaler HT, DeAngelis LM, Abrey LE. Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? J Neurooncol 2002; 58: 175–178.
32. Batchelor T, Carson K, O'Neill A et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol 2003; 21: 1044–1049.
33. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002; 20: 4643–4648.
34. Alvarnas JC, Negrin RS, Horning SJ et al. High-dose therapy with hematopoietic cell transplantation for patients with central nervous system involvement by non-Hodgkin's lymphoma. Biology of Blood and Marrow Transplantation 2002; 6: 352–358.
35. Illerhaus G, Müller F, Feuerhake F, Schäfer AO, Ostertag C, Finke J. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. Haematologica 2008; 93, 147–148.
36. Ferreri AJ, Reni M, Foppoli M et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 2009; 374: 1512–20.
37. Rubenstein JL, Hsi ED, Johnson JL et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol 2013; 31: 3061–3068.
38. Colombat P, Lemevel A, Bertrand P et al. High-dose chemotherapy with autologous stem cell transplantation as first-line therapy for primary CNS lymphoma in patients younger than 60 years : a multicenter phase II study of the GOELAMS group. Bone Marrow Transplantation 2006; 38: 417–420.
39. Chen Y-B, Batchelor T, Li S et al. Phase 2 trial of high-dose rituximab with high-dose cytarabine mobilization therapy and high-dose thiotepa, busulfan, and cyclophosphamide autologous stem cell transplantation in patients with central nervous system involvement by non-Hodgkin lymphoma. Cancer 2015; 121: 226–233.
40. Omuro A, Correa DD, DeAngelis LM et al. R-MPV followed by high--dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood 2015; 125: 1403–1410.
41. Ferreri AJ, Cwynarski K, Pulczynski E et al. Addition of thiotepa and rituximab to antimetabolites significantly improves outcomes in primary CNS lymphoma: first randomization of the IELSG32 trial. Hematol Oncol 2015; 33: 103–104, 109.
42. Schorb E, Kasenda B, Atta J et al. Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. Haematologica 2013; 98: 765–770.
43. Batchelor TT, Grossman SA, Mikkelsen T, Ye X, Desideri S, Lesser GJ. Rituximab monotherapy for patients with recurrent primary CNS. Neurology 2011; 76: 929–930.
44. Yamamoto W, Tomita N, Watanabe R et al. Central nervous system involvement in diffuse large B-cell lymphoma. Eur J Haematol 2010; 85: 6–10.
45. Holdhoff M, Ambady P, Abdelaziz A et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology 2014; 83: 235–239.
46. Rubenstein JL, Fridlyand J, Abrey L et al. Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. J Clin Oncol 2007; 25: 1350–1356.
47. Plotkin SR, Betensky RA, Hochberg FH et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. Clin Cancer Res 2004; 10: 5643–5646.
48. Nguyen PL, Chakravarti A, Finkelstein DM, Hochberg FH, Batchelor TT, Loeffler JS. Results of whole-brain radiation as salvage of methotrexate

failure for immunocompetent patients with primary CNS lymphoma. J Clin Oncol 2005; 23: 1507–1513.
49. Soussain C, Hoang-Xuan K, Taillandier L et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societé Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. J Clin Oncol 2008; 26: 2512–2518.
50. Soussain C, Choquet S, Fourme E et al. Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. Haematologica 2012; 97: 1751–1756.
51. Korfel A, Elter T, Thiel E et al. Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas. Haematologica 2013; 98: 364–370.
52. Illerhaus G, Fritsch K, Schmidt-Wolf I et al. High dose-chemotherapy followed by autologous peripheral blood stem cell transplantation for patients with refractory or recurrent primary central nervous system lymphoma — results of a multicenter study by the Germany Collaborative PCNSL Study Group. Blood 2014; 124: 2527.
53. Wang CC, Carnevale J, Rubenstein JL. Progress in central nervous system lymphoma. Br J Haematol 2014; 166: 311–325.