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Primary CNS Lymphoma in Immunocompetent Patients

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) constitutes a rare group of extranodal non-Hodgkin's lymphomas (NHLs), primarily of B cell origin, whose incidence has markedly increased in the last three decades. Immunodeficiency is the main risk factor, but the large majority of patients are immunocompetent. Recent evidence suggests a specific tumorigenesis that may explain their particular clinical behavior compared with systemic NHL. The addition of i.v. high-dose methotrexate (MTX) chemotherapy to whole-brain radiotherapy (WBRT) has considerably improved the prognosis, leading to a threefold longer median survival time compared with WBRT alone and represents the current standard of care. However, this combined treatment exposes the patient, especially the elderly, to a high risk for delayed neurotoxicity. In the older population (>60 years), there is growing evidence that MTX-based chemotherapy alone as initial treatment is the best approach to achieve effective tumor control without compromising patient quality of life. In the younger population, the risk for neurotoxicity is much lower, and this strategy is controversial because it may be associated with higher relapse rates. Future efforts should focus on the development of new polychemotherapy regimens allowing the reduction or deferral of WBRT in order to minimize the risk for delayed neurotoxicity. In this setting, intensive chemotherapy with autologous blood stem cell transplantation was recently demonstrated to be feasible and efficient as salvage therapy and is currently being evaluated as part of primary treatment. This review highlights the recent advances in the pathogenesis and treatment of PCNSL in the immunocompetent population. *The Oncologist* 2009;14: 526–539

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Introduction

Primary central nervous system lymphomas (PCNSLs) are extranodal malignant lymphomas arising within the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma at the time of diagnosis. The incidence of PCNSL in western countries is five per one million person-years. Currently PCNSL are estimated to account for up to 1% of non-Hodgkin lymphomas (NHLs) and 3%–5% of all primary brain tumors. After a continual increase over the past two decades [1], epidemiologic data suggest a recent decrease in the incidence of PCNSL, particularly among young patients suffering from AIDS, probably associated with the development of new active antiviral drugs. In contrast, the incidence remains high among older patients (>60 years) who are mostly immunocompetent [2]. The reason for the rising incidence of PCNSL among the immunocompetent population is obscure. PCNSL is also of interest because it is the primary malignant brain tumor whose prognosis has improved the most over the past two decades as a result of a better treatment strategy. Although the prognosis remains poor for the majority of patients, a substantial minority, representing approximately 20%–30% of cases, can hope to be cured. Because long-term survivors are at a higher risk for developing severe delayed cognitive dysfunctions, future treatment should improve efficacy while limiting the risk for neurotoxicity. This review focuses on PCNSL in the immunocompetent population

Pathology and Pathogenesis

In immunocompetent patients, all but 5% of PCNSLs are diffuse large B-cell lymphomas (DLBCLs) [3]. Because they are morphologically indistinguishable from systemic DLBCLs, the World Health Organization classification of tumors of hematopoietic and lymphoid tissues does not recognize PCNSL as a separate entity [4]. The remaining cases of PCNSL are T-cell lymphomas (2%–5%) [5] or, in rare instances, low-grade B-cell lymphomas of the lymphoplasmocytic (Waldenström macroglobulinemia), follicular, or mucosa-associated lymphoid tissue type [6]. Little is known about the tumorigenesis of PCNSL. In contrast to immunocompromised patients, the Epstein-Barr virus does not appear to be involved in the pathogenesis of PCNSL in immunocompetent patients. The site of origin of lymphoma cells and the biological mechanisms involved in the neoplastic transformation of the cells and their intriguing confinement within the CNS during the course of the disease have yet to be elucidated. Indeed, the CNS does not contain resident lymphocytes under normal circumstances and lacks lymphatic vessels. However, recent evidence suggests that T and B cells enter the CNS under physiological conditions and it has been hypothesized that PCNSL may originate from B cells derived from systemic lymphoid tissues normally trafficking in and out of the CNS [7]. PCNSL could derive from a benign CNS inflammatory process through a monoclonal proliferation of B cells. Another hypothesis is that PCNSL might represent the metastasis of an occult systemic lymphoma, eradicated by an intact immune system but escaping within the immune-privileged CNS. Analysis of clonally rearranged IgH genes revealed identical dominant polymerase chain reaction products in bone marrow aspirates, blood samples, and tumor specimens from some PCNSL patients, suggesting that subclinical systemic disease can be detected at the initial diagnosis, in favor of a systemic origin of the tumor in these cases [8]. In addition, B-cell tropism for the CNS might be acquired (before or after the oncogenic events) through specific interactions between selective homing receptors and their ligands expressed on CNS endothelial cells, as suggested by the distinctive angiotropism of CNS lymphoma cells. Different inflammatory (e.g., CCL2) and homeostatic (e.g., CCL19, CCL21, CXCL12, and CXCL13) chemokines might contribute to B-cell migration into the CNS [9, 10].

It also remains unclear whether the dismal outcome of PCNSL patients compared with patients with systemic DLBCL is attributable to the immune-privileged cerebral location or reflects a specific aggressive intrinsic biologic behavior. Recently, expression profiling and genomic screening have provided new insight into understanding the poor prognosis of PCNSL patients. Based on lymphochip cDNA microarrays, two distinct gene expression profiles have been identified among systemic DLBCLs, indicative of different stages of B-cell differentiation. One subgroup expressed genes characteristic of germinal center B cells (GCB subgroup), whereas the other expressed genes normally induced during in vitro activation of peripheral blood B cells (ABC subgroup). Interestingly, patients with the GCB signature had a significantly better outcome than those with the ABC profile [11]. PCNSLs have been shown to frequently express BCL-6 [12] and to carry an extremely high load of somatic mutations of immunoglobulin genes and several oncogenes demonstrating aberrant ongoing hypermutation [13–15]. Because such ongoing hypermutation and BCL-6 expression are considered as germinal center (GC) markers, it has been postulated that the cell of origin of PCNSL passes through the GC microenvironment and that these neoplasms correspond to the GCB subgroup as defined for DLBCL. However, recent immunoprofiling [16] and gene expression studies using cDNA microarrays [17, 18] demonstrated that PCNSL may exhibit characteristics associated with both the ABC and GCB subtypes. Thus, PCNSLs may correspond to an overlapping B-cell

differentiation time slot, that is, the late GC/early post-GC stage.

Pangenomic analyses of chromosomal imbalances by comparative genomic hybridization have shown frequent chromosome 6q loss (60%–75%) in PCNSL patients [19–21]. Nakamura et al. [22] refined the candidate region suspected to contain a lymphoma-related tumor suppressor gene in the 6q22–23 locus by a fine loss of heterozygosity deletion mapping of 6q in PCNSL. The *PTPRK* gene seems a relevant candidate gene, because it is involved in the regulation of cell contact and adhesion, and a loss of protein expression was observed in most (76%) of the PCNSLs tested. The protein that this gene encodes belongs to the protein tyrosine phosphatase superfamily of enzymes. Further studies to identify gene mutations and/or rearrangements are needed to ascertain the involvement of *PTPRK* in PCNSL tumorigenesis. Interestingly, the authors showed that chromosome 6q loss was found at a significantly higher rate in PCNSL than in systemic DLBCL and was correlated with shorter survival [22]. An independent study of 75 newly diagnosed HIV-negative PCNSL patients investigated by interphase fluorescence in situ hybridization analysis confirmed frequent del(6)(q22) chromosome deletion, with a prevalence of 45%, and its negative impact on overall survival (OS) [23]. Chromosome 6q loss therefore represents a prognostic marker in PCNSL. Further, the *BCL-6* gene has been found to be mutated and its chromosomal locus (3q27) is often translocated (20%), suggesting that *BCL-6* activation through genomic rearrangements may play a role in PCNSL pathogenesis [23–25]. *BCL-6* is frequently expressed in PCNSL, but there are conflicting data on its prognostic value as an immunohistochemical marker [16, 26–29].

Together, these results provide evidence for a different pathogenesis in PCNSL than in DLBCL, explaining in part its particular clinical behavior and dismal prognosis.

Diagnosis and Workup

The clinical presentation of PCNSL patients includes focal symptoms and raised intracranial pressure, but behavioral and personality changes and confusion frequently occur in the elderly. Its deep location explains why seizures are less frequent than in other brain tumors [30, 31]. Computed tomography (CT) scans and magnetic resonance imaging (MRI) typically show unique or multiple periventricular, homogeneously enhancing lesions [32–34]. But PCNSL is potentially associated with a large spectrum of radiological presentations and can simulate inflammatory (sarcoidosis, multiple sclerosis) or infectious (acute disseminated encephalomyelitis) diseases or other brain tumors (meningiomas, malignant gliomas, gliomatosis cerebri, brain metastases) [35–37] (Fig. 1). The diagnosis may be difficult to establish, especially with the presence of nonenhancing infiltrating lesions (occurring in about 10% of cases) [38, 39]. Magnetic resonance spectroscopy and perfusion MRI seem helpful tools when showing some suggestive abnormalities [40–42]. Steroid-induced and rare spontaneous disappearance of lesions is classic, hence the term ghost tumors [43, 44]. Ring-like enhancement is rare in immunocompetent patients. However, none of these signs are specific, and the diagnosis relies on the pathological study of a tumor sample. Cerebral biopsy can be avoided when lymphomatous cells are discovered in the cerebrospinal fluid (CSF) (10%–30% of patients) or in a vitreous-body biopsy (uveitis, sometimes asymptomatic, is present in 10%–20% of cases at diagnosis). The current recommended staging evaluations for PCNSL include full-body CT scans and bone marrow biopsy [45]. In fact, systemic involvement is so rare at onset that extensive staging is not recommended by some authors, who only require HIV testing, chest radiography, analysis of CSF, and ocular slit-lamp ex-

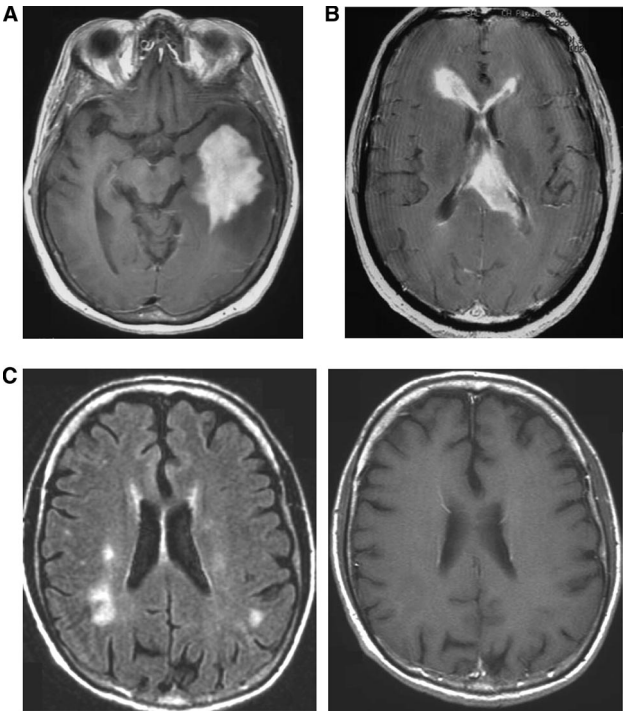

Figure 1. Examples of PCNSL radiological presentations. **(A):** PCNSL presenting as a left temporal space–occupying lesion: MRI axial T1-weighted sequence with gadolinium. **(B):** PCNSL presenting as a tumoral ventriculitis: MRI axial T1-weighted sequence with gadolinium. **(C):** PCNSL presenting as nonenhancing lesions: *Left*: multiple signal hyperintensities in the white matter on MRI axial flair weighted sequence; *Right*: no contrast enhancement on axial gadolinium T1-weighted sequence.

Abbreviations: MRI, magnetic resonance imaging; PCNSL, primary central nervous system lymphoma.

amination, and a careful clinical assessment. However, in a recent retrospective study, 7% of patients were found to have systemic NHL by staging full-body fluorodeoxyglucose positron emission tomography when full-body CT scans and bone marrow biopsies were negative [46]. This higher incidence of systemic lymphoma than reported in prior series suggests that occult lymphoma may be more common than previously recognized. These findings warrant prospective validation, because the identification of a systemic site of the lymphoma has important implications in the management of PCNSL.

Prognostic Factors

Age and performance status are the main independent prognostic factors consistently identified in a large number of studies. In order to provide a predictive model that will determine patient prognosis and help in therapeutic decision making, several prognostic scoring systems were recently proposed. The International Extranodal Lymphoma Study Group prognostic index (0–5 scale) includes five independent variables: age, performance status, lactate dehydrogenase level, CSF protein, and involvement of deep structures [47]. The Nottingham/Barcelona score (0–3 scale) proposes a prediction score calculated from three independent prognostic factors: age, performance status, and extent of brain disease [48]. The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score is based solely on age and Karnofsky performance status score variables and includes three classes [49].The clinical relevance of these prognostic scores should be validated in further studies to facilitate comparison among phase II trials.

Treatment of Newly Diagnosed PCNSL

PCNSL is a highly radiosensitive and chemosensitive infiltrative tumor, and surgery is therefore restricted to diagnostic biopsy. Although the tumor appears on MRI as a unique contrast-enhancing lesion in the majority of immunocompetent patients, whole-brain radiotherapy (WBRT) is recommended based of the microscopically diffuse nature of PCNSL. Despite a high rate of response, radiotherapy (RT) alone provides limited survival benefit in PCNSL patients, with a median OS duration of 10–18 months and a 5-year survival rate <5% [50]. The only phase II trial, conducted by the Radiation Therapy Oncology Group (RTOG), which delivered a total dose of 40 Gy with an additional 20-Gy boost to contrast-enhancing lesions, reported an 11.6-month OS time [51]. Interestingly, most of the relapses occurred in sites that had received the maximum RT dose. These disappointing results have led to the use of chemotherapy in combination with WBRT. Since the 1990s, numerous convergent phase II studies have shown that the addition of high-dose methotrexate (MTX)-based chemotherapy to RT results in a substantially longer survival time than with RT alone (median survival time, 2–4 years; 5-year survival rate, 20%–40%) (Table 1) [52–67]. In contrast, adding standard chemotherapy for systemic lymphoma, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (the CHOP regimen), to RT did not appear to result in longer survival than with RT alone. The fact that these regimens failed to produce longer survival than with RT alone may reflect the poor CNS penetration of the chemotherapeutic agents included in these regimens. The optimal dose of postchemotherapy irradiation has never been prospectively investigated. Doses of 20–50 Gy to the whole brain with or without a tumor bed boost are currently used, with most of the protocols using a total dose of 40–45 Gy without a boost. For patients who achieve a complete response (CR) after high-dose MTX-based chemotherapy, it remains unclear whether consolidation with WBRT provides better disease control or survival. A subset analysis from a phase II trial that included 25 patients aged <60 years who achieved a CR after initial chemotherapy and received either 45 Gy or 30.6 Gy as consolidation treatment showed a significantly higher recurrence rate and lower OS rate in the reduced-dose RT group [59]. Other studies did not share this observation. In two multicenter retrospective analyses no differences were noted regarding disease-free survival or OS times between patients in CR receiving WBRT as consolidation treatment and those receiving WBRT at the time of relapse [68, 69]. In the MSKCC experience, consolidation treatment with WBRT produced a longer failure-free survival time but not OS time in CR patients after MTX-based therapy and produced higher rates of neurotoxicity [70].

In order to reduce neurotoxicity, several groups have explored the efficacy of various high-dose MTX-based chemotherapy regimens as initial treatment for newly diagnosed PCNSL patients. Neuwelt et al. [71] developed the first such approach using an intra-arterial MTX-based chemotherapy protocol associated with blood-brain barrier (BBB) disruption in order to enhance drug delivery to the brain. However, despite encouraging results in terms of survival and tolerance [71, 72], the complexity of the procedure restricts its use to experienced centers. A German prospective multicenter trial using a regimen (Bonn protocol) that included i.v. high-dose MTX (5 g/m^2), high-dose cytarabine, ifosfamide, cyclophosphamide, vincristine, vindesine, and intraventricular chemotherapy reported a 71% response rate and an extended median survival duration of 50 months [73]. Of note, this vigorous regimen was associated with a high rate of acute toxicities, including a 9% toxic death rate, but delayed neurotoxicity occurred in

Table 1. Literature review: Combined MTX-based chemoradiotherapy

Study	*n*	Chemotherapy	WBRT + boost	CR + PR (%) after CT	Median PFS (mos)	MS (mos)	Neurotoxicity
Gabbai et al. (1989) [52]	13	MTX (3 g/m^2)	30–44 Gy	61 + 31	–	9+	–
DeAngelis et al. (1992) [53]	31	MTX (1 g/m^2), i.t. CT, Ara-C	40 Gy + 14 Gy	0 + 64	–	42	–
Glass et al. (1994) [54]	25	MTX (3.5g/m^2)	30–55 Gy	56 + 32	–	33	8%
Blay et al. (1995) [55]	25	MTX (3 g/m^2), CTX, ADR, VCR, Ara-C, i.t. CT	20 Gy + 30 Gy	56 + 16	–	>24	–
Glass et al. (1996) [56]	18	MTX (3.5 g/m^2), CHOD	30–60 Gy	61 + 17	19	25	11%
Brada et al. (1998) [57]	31	MTX (0.5–2 g/m^2), CTX, ADR, VCR	40–65 Gy	33 (CR)	–	23	10%
O'Brien et al. (2000) [58]	46	MTX (1 g/m^2)	45 Gy + 5 Gy	82 + 13	17	33	13%
Bessel et al. (2002) [59]	57	MTX (1.5 g/m^2), Ara-C, BCNU, VCR, CHOD	45 or 30 Gy	63 + 10		40	12%
De Angelis et al. (2002) [60]	102	MTX (2.5 g/m^2), PCB, VCR, i.t. CT, Ara-C	45 Gy	58 + 36	24	37	¨15%
Poortmans et al. (2003) [61]	52	MTX (3 g/m^2), BCNU, TNP, i.t. CT	40 Gy	32 + 40	–	46	14%
Omuro et al. (2005) [62]	17	MTX (1 g/m^2), PCB, TTP	40 Gy	41 + 41	18	32	30%
Korfel et al. (2005) [63]	56	MTX (1.5 g/m^2), BCNU, PCB, with or without IDA/IFO with or without Ara-C	With or without 45 Gy	61 (CR)	10	11	18%
Ferreri et al. (2006) [64]	41	MTX (3.5 g/m^2), Ara-C, IDA, TTP	40 Gy	44 + 32	13	15	–
Abrey et al. (2000) [65]; Gavrilovic et al. (2006) [66]	57	MTX (3.5 g/m^2), PCB, Ara-C, i.t. CT	With or without 45 Gy	56 + 33	–	51	30%
Shah et al. (2007) [67]	30	Rituximab, MTX (3.5 g/m^2), PCB, VCR	23.4 or 45 Gy	78 + 15	40	>37	–

Abbreviations: ADR, doxorubicin; Ara-C, cytarabine; CHOD, CTX, ADR, VCR, and dexamethasone; CR, complete response; CT, chemotherapy; CTX, cyclophosphamide; IDA, idarubicin; IFO, ifosfamide; MS, median survival; MTX, methotrexate; PCB, procarbazine; PFS, progression-free survival; PR, partial response; TNP, teniposide; TTP, thiotepa; VCR, vincristine; WBRT, whole-brain radiotherapy.

only 3% of cases. In France, a multicenter study conducted by the Association des Neuro-Oncologues d'Expression Française (ANOCEF) group treated patients aged <60 years with a combination of drugs, including MTX (3 g/m^2), lomustine (CCNU), procarbazine, and intrathecal chemotherapy (MTX, cytarabine); consolidation therapy either with WBRT or intensive chemotherapy was deferred in responding patients (90%). This regimen was well tolerated. Although a similar median OS time (>54 months) and neurotoxicity rate (9%) were reported, this regimen was associated with a shorter median progression-free survival (PFS) duration (13 months) [74]. Together, these results contribute to the existing literature (Table 2) [71, 73–77], suggesting that a chemotherapy alone plus deferred RT strategy may result in a shorter PFS time but allow survival results comparable with those reported for combined chemo-RT, with better neurocognitive and quality of life effects. This supports the comparison of these approaches in a prospective randomized trial, as proposed by the ongoing German G-PCNSL-SG-1 phase III study. Whereas high-dose MTX is undoubtedly a key drug for PCNSL chemotherapy, interest in adding other agents to MTX exists in the scientific community. Two prospective phase II trials have investigated the efficacy of high-dose MTX (8 g/m^2) as a single-drug therapy. The New Approaches to Brain Tumor Therapy trial [76] and the German Neuro-Oncology Working Group (NOA)-3 trial [77] demonstrated a similarly low median PFS duration (13 months), clearly shorter

Table 2. Literature review: Chemotherapy alone

Study	*n*	Chemotherapy	CR + PR (%)	PFS (mos)	MS (mos)	Neurotoxicity
Neuwelt et al. (1991) [71]	17	MTX i.a. (2.5 g), PCB, CTX	81 + 19	–	44	0%
Sandor et al. (1998) [75]	14	MTX (8 g/m^2), TTP, VCR, i.t. CT	79 + 21	16	>40	14%
Batchelor et al. (2003) [76]	25	MTX i.v. (8 g/m^2)	52 + 22	12	>23	0%
Pels et al. (2003) [73]	65	MTX (5 g/m^2), VCR, IFO, CTX, Ara-C, i.t. CT	61 + 10	21	50	3%
Herrlinger et al. (2005) [77]	37	MTX (8 g/m^2)	29 + 5	10	25	20%
Omuro et al. (2006) [74]	64[a]	MTX (3 g/m^2), CCNU, PCB, with or without i.t. CT	52 + 38	13	>54	9%

[a] Patients aged <60 years.
Abbreviations: Ara-C, cytarabine; CR, complete response; CT, chemotherapy; CTX, cyclophosphamide; IFO, ifosfamide; MS, median survival; MTX, methotrexate; PCB, procarbazine; PFS, progression-free survival; PR, partial response; TTP, thiotepa; VCR, vincristine.

than that achieved with a polychemotherapy regimen. This suggests that other cytotoxic agents should be combined with high-dose MTX in a chemotherapy-alone approach. However, the optimal combination remains to be established. Alkylating agents able to effectively penetrate the CNS are preferred. Concerning the optimal "high dose" of MTX to deliver, although there is no clear evidence of a dose–response relationship, a dose ≥3 g/m^2 in a rapid infusion is recommended [78]. In addition, this dose generally yields cytotoxic levels in the CSF thus theoretically avoiding the need to administer intrathecal chemotherapy for leptomeningeal coverage. In practice, when i.v. high-dose MTX (>3 g/m^2) is used, several authors recommend adding intrathecal chemotherapy only in cases of positive CSF cytology and withholding it in the absence of detectable subarachnoid disease [79]. However, other authors recently reported a higher rate of early relapse after eliminating intraventricular chemotherapy from their initial protocol despite the use of high-dose i.v. MTX (5 g/m^2) (modified Bonn protocol) [80]. The role of intrathecal prophylaxis warrants investigation in a prospective trial.

Delayed Neurotoxicity

WBRT, high-dose MTX chemotherapy, and the combination of these two treatments expose patients to delayed neurotoxicity. This complication occurs as early as 3 months after treatment and is characterized by attention deficit, memory impairment, ataxia, and urinary incontinence, potentially ultimately leading to dementia. Imaging shows confluent diffuse white matter changes and later cortical–subcortical atrophy. The physiopathology of this complication remains poorly understood; loss of oligodendrocyte progenitors and oxidative stress have been suggested as potential mechanisms. Lai et al. [81] reported a well-documented series of five autopsied cases who died of treatment-related leukoencephalopathy. All had combined treatment and were in tumor remission. In addition to white matter rarefaction and spongiosis, fibrotic thickening of small vessels in the deep white matter and atherosclerosis of intracranial large vessels were systematically found, suggesting that a vascular process also may be an important component of this white matter injury. The risk for neurotoxicity increases sharply with patient age. In the elderly population (patients aged >60), virtually all long-term survivors develop delayed neurotoxicity, with its devastating quality of life consequences and fatality, after combined treatment [82]. In the younger population (patients aged <60), the exact incidence of this complication is more difficult to determine. Cognitive dysfunctions are usually less severe, although they do interfere with quality of life, and occur later than in the elderly population [62]. An update of the MSKCC experience that provided long-term data (median follow-up, 115 months) reported a 26% rate of neurotoxicity in surviving patients aged <60 years (versus 75% in the elderly) [66]. However, this should be regarded as a minimum estimate in the absence of a psychometric evaluation. A series of 19 consecutive young patients (median age, 44 years) treated in a European clinical trial and in complete remission for a mean duration of 24 months after combined therapy was investigated by extensive neuropsychological evaluation [83]. Cognitive impairments were found in 63% of patients (including 21% with severe cognitive deficits), only 42% of the patients resumed work, and 67% of the patients had white matter abnormalities and cortical atrophy detectable on MRI. Although this study suffers from the absence of available baseline data at the completion of treatment to assess the potential contribution of the tumor to cognitive dysfunction, it suggests that the

incidence of delayed neurotoxicity after combined therapy is largely underestimated in young patients, though less severe than in the elderly. These results contrast sharply with a prospective neuropsychological study performed by Fliessbach et al. [84] in a series of 23 patients successfully treated with a high-dose MTX-based chemotherapy regimen without RT (median age, 54 years; range, 28–68). Comparison between a baseline evaluation at the completion of treatment and at the last follow-up (median, 44 months) showed good preservation of cognitive functions, although one third of the patients demonstrated some degree of white matter changes on MRI. This latter point confirmed some previously published reports showing that MTX-related leukoencephalopathy is frequent but not necessarily well correlated with cognitive performance [85]. The significantly better preservation of neurocognitive functions and quality of life observed in patients treated with chemotherapy alone compared with those who received combined treatment was also supported by Correa et al. [86] in a retrospective comparative neuropsychometric analysis of 28 patients from a single institution. The incorporation of systematic psychometric and quality of life evaluations with an appropriate standardized test battery was recommended for all future prospective trials [87]. Interestingly, some functional polymorphisms interfering with methionine metabolism might influence MTX neurotoxicity [88, 89].

Treatment in the Elderly

Elderly patients (i.e., those aged ≥60 years), who experience a very poor prognosis and high vulnerability to delayed neurotoxicity, represent an important subgroup, accounting for approximately half of all cases of PCNSL. However, prospective trials specifically devoted to older patients are scarce. Most of the available data come from retrospective studies (Table 3) [51, 60, 65, 66, 72, 73, 90–99]. In the elderly, PCNSLs exhibit low radiosensitivity; an RTOG phase II trial reported a short median survival time of 7.6 months with RT alone [51]. The high risk for neurotoxicity observed with the combined chemo-RT approach (see above) prompted several authors to defer RT in such populations. The only multicenter phase II trial focusing on patients aged >60 and evaluating chemotherapy alone as initial treatment was conducted by the European Organization for Research and Treatment of Cancer (EORTC). The regimen consisted of high-dose MTX (1 g/m^2) plus lomustine (CCNU), procarbazine, and intrathecal chemotherapy (MTX, cytarabine). The intent-to-treat response rate and median survival time were 48% and 14.3 months, respectively [97]. Although that study showed less favorable results than those reported by other published studies (median survival time in the range of 18–34 months) [66, 72, 73, 94–99], it nevertheless led to the same conclusions and confirmed that chemotherapy alone is a valuable approach for treating elderly patients with PCNSL. Because the median PFS time was similar to that in other studies, the shorter OS time may be explained by the salvage therapy. Hence, in the EORTC trial, only a small minority of patients were treated with WBRT at relapse. Together, chemotherapy alone appears to be more effective than RT alone and considerably reduces the risk for neurotoxicity (up to 8% of cases) compared with that expected with combined treatment, allowing a substantial proportion of patients to reach prolonged remission without the need for consolidation RT and preserving their quality of life. Future protocols for the elderly should focus on defining the optimal chemotherapy regimen.

Intensive Chemotherapy with Autologous Stem Cell Transplantation

Intensive chemotherapy (ICT) with autologous stem cell transplantation (ASCT) is the standard treatment for chemosensitive relapsing systemic NHL. Because ICT is expected to improve BBB crossing, allowing cytotoxic agents to reach the brain at higher doses, this strategy has been evaluated for PCNSL. This procedure was first evaluated in refractory and recurrent cerebral and intraocular lymphoma with promising results in a single-institution pilot study [100]. The protocol consisted of an induction cytarabine–etoposide combination (the CYVE regimen) followed by high-dose chemotherapy with thiotepa, busulfan, and cyclophosphamide (the TBC regimen). These results were recently confirmed in a multicenter phase II trial using the same regimen and including 43 patients [101]. Twenty-seven patients (62% by the intention-to-treat analysis) completed the full ICT–ASCT procedure, including 15 responsive and 12 nonresponsive patients to CYVE induction salvage chemotherapy. Twenty-six of these 27 patients achieved a CR with prolonged remission; the median PFS and OS times were 41 and 58 months, respectively. Interestingly, all but one patient in whom the disease was refractory to salvage chemotherapy achieved a CR after ICT–ASCT (Fig. 2). The intent-to-treat median PFS and OS times of the whole population of this trial were 11 and 18 months, respectively. Together, these results compare favorably with those reported for other salvage treatments, including second-line conventional chemotherapy regimens [102, 103] and RT alone [104, 105]. The favorable impact of ICT–ASCT on survival, regardless of the chemosensitivity status before ICT, which contrasts with what is reported in relapsing systemic NHLs, suggests that ICT–ASCT might overcome resistance mediated by the BBB.

Table 3. Literature review: Treatment of the elderly

Study	*n*	Chemotherapy regimen	WBRT	PFS (mos)	MS (mos)	Neurotoxicity
Radiotherapy alone						
Nelson et al. (1992) [51]	17	No	40 Gy + 20 Gy	–	7	–
Chemoradiotherapy						
Schultz et al. (1996) [90]	34	CHOD	41 Gy + 18 Gy	–	10	–
O'Neill et al. (1995) [91]	36	CHOP, Ara-C	50 Gy	6.5	9	–
Desablens et al. (1999) [92]	76	MTX (3 g/m^2), teniposide, BCNU	40 Gy	–	18	48%
Bessel et al. (2001) [93]	14	MTX (1.5 g/m^2), CHOD, BCNU, Ara-C	45 Gy + 10 Gy	–	23	62%
De Angelis et al. (2002) [60]	41	MTX (2.5 g/m^2), PCB, VCR	36–45 Gy	11	21	19%
Abrey et al. (2000 [65]; Gavrilovic et al. (2006) [66]	12	MTX (3.5 g/m^2), PCB, VCR, Ara-C	45 Gy	–	29	75%
Chemotherapy alone						
Freilich et al. (1996) [94]	13	MTX (1–3 g/m^2), PCB with or without VCR, TTP, Ara-C	No	–	30	7%
Ng et al. (2000) [95]	10	MTX i.v. (8 g/m^2)	No	–	36	0%
McAllister et al. (2000) [72]	38	MTX i.a. (2.5 g/m^2), CTX, VP16	No	–	16	0%
Pels et al. (2003) [73]; Juergens et al. (2006) [96]	35	MTX (5 g/m^2), VCR, IFO, CTX, Ara-C, i.t. CT	No	9	36	6%
Hoang-Xuan et al. (2003) [97]	50	MTX (1 g/m^2), PCB, CCNU, i.t. CT	No	6.8	14	8%
Abrey et al. (2000) [65]; Gavrilovic et al. (2006) [66]	22	MTX (3.5 g/m^2), PCB, VCR, Ara-C	No	7	29	11%[a]
Omuro et al. (2007) [98]	23	MTX (3 g/m^2), temozolomide	No	8	35	–
Zhu et al. (2009) [99]	31[a]	MTX (3.5–8 g/m^2)	No	7	37	0%

[a] Patients aged >70 years.
Abbreviations: Ara-C, cytarabine; CHOD, CTX, doxorubicin, VCR, and dexamethasone; CHOP, cyclophosphamide, doxorubicin, VCR, and prednisone; CT, chemotherapy; CTX, cyclophosphamide; IFO, ifosfamide; MS, median survival; MTX, methotrexate; PCB, procarbazine; PFS, progression-free survival; TTP, thiotepa; VCR, vincristine; WBRT, whole-brain radiotherapy.

Several studies have evaluated ICT–ASCT as first-line treatment in newly diagnosed PCNSL patients (Table 4) [100, 101, 106–111]. The BEAM protocol (BCNU, etoposide, cytarabine, and melphalan) and high-dose thiotepa-based chemotherapy were used as conditioning regimens and resulted in a higher rate of complete remission after high-dose MTX-based induction chemotherapy. However, three of these trials included WBRT at the end of the procedure, making an analysis of the specific contribution of ICT–ASCT to the encouraging survival results questionable. Subsequently, in order to minimize the risk for neurotoxicity, Illerhaus et al. [111] modified their initial protocol by increasing the number of chemotherapy cycles and augmenting the thiotepa dose within the conditioning regimen while restricting WBRT to patients not in CR after finishing chemotherapy. In addition, they delivered ICT–ASCT to all of their patients irrespective of their response to high-dose MTX. The preliminary results of that pilot study support the hypothesis that WBRT may not be necessary to cure many patients in CR after ICT–ASCT. The only trial that did not combine RT with ICT–ASCT used an induction high-dose MTX–cytarabine chemotherapy regimen followed by an intensive BEAM regimen [106]. The results were disappointing, with a short median event-free survival time (9.3 months). This suggests that the drugs were used at suboptimal doses and that more aggressive regimens, including agents such as thiotepa and busulfan that penetrate the CNS, rather than standard lymphoma regimens may be warranted. This may be illustrated by encouraging results reported by Cheng et al. [107] using the TBC pretransplant conditioning regimen without WBRT in a small series of seven patients with a median event-free survival duration that was not reached at 24 months.

The evaluation of the neurocognitive tolerance of this

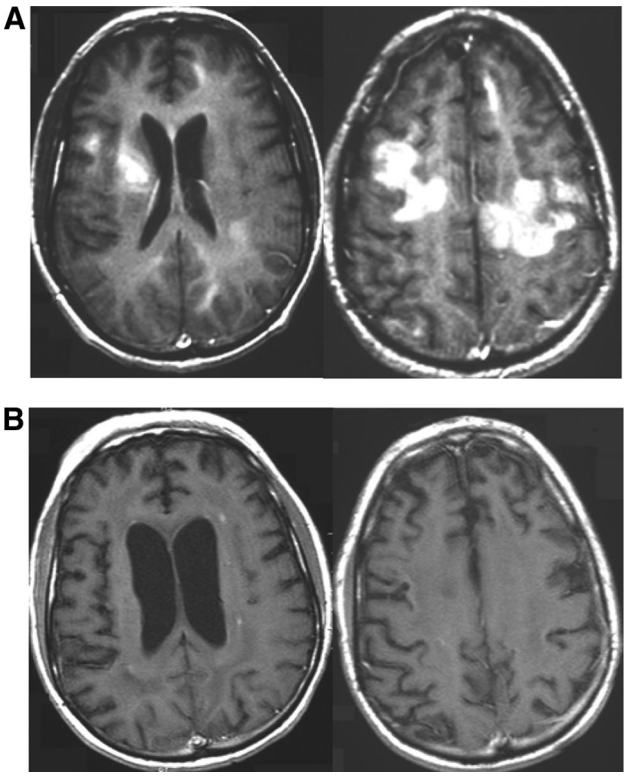

Figure 2. MRI T1-weighted sequence with gadolinium injection. **(A):** Patients suffering from progressive PCNSL refractory to combined high-dose MTX-based polychemoradiotherapy and salvage chemotherapy (high-dose cytarabine-VP16). **(B):** Objective response to intensive chemotherapy (thiotepa–busulfan–cyclophosphamide regimen) with autologous stem cell transplantation.

Abbreviations: MRI, magnetic resonance imaging; MTX, methotrexate; PCNSL, primary central nervous system lymphoma.

approach is an important issue. Soussain et al. [100, 101] observed a 10%–30% rate of neurotoxicity in relapsing patients treated with ICT–ASCT as salvage therapy, especially in older and preirradiated patients. In the studies using a combined approach, that is, ICT–ASCT followed by WBRT, for newly diagnosed PCNSL, the reported rates of severe neurotoxicity are in the range of 0%–20% [109–111]. In contrast, this was not reported in the two studies using ICT–ASCT without WBRT as primary treatment [106, 107]. Further prolonged neurocognitive follow-up with psychometric evaluation is clearly needed. Neurotoxicity seems to be influenced by the age of the patient, prior treatment, especially RT, and the CNS safety profile of the drug used. It remains to be determined whether ICT–ASCT can represent an interesting alternative option to RT as consolidation treatment. A randomized trial for patients aged <60 years, comparing WBRT with ICT-ASCT (TBC regimen) as a consolidation treatment after high-dose MTX-based induction chemotherapy, with special attention on neurocognitive follow-up is currently ongoing, coordinated by a French Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang–ANOCEF intergroup.

Salvage Treatment

Although combined treatment has considerably improved the prognosis for PCNSL patients, one should not forget that about one third of patients are refractory to initial treatment and that the majority of patients who have achieve complete remission subsequently relapse. As discussed above, the most promising results have been reported with ICT–ASCT. Conventional second-line chemotherapy, such as temozolomide (TMZ) [104], topotecan [112], intra-arterial carboplatin [113], and high-dose cytarabine combined with etoposide and ifosfamide [102], has been also shown to be potentially active in relapsed PCNSL. These latter treatments achieved objective response rates of 26%–37%, 1-year PFS rates of 13%–22%, and 1-year OS rates of 25%–41%. Although the activity of TMZ and topotecan as single agents is modest in relapsed tumors, their role as part of a first-line MTX-based combination merits further investigation [98], particularly because of their relatively good safety profile. MTX reinduction may also yield new remission in some patients who previously achieved prolonged remission with high-dose MTX-based chemotherapy [114]. Two studies recently evaluated the activity and tolerance of WBRT delivered in relapsed PCNSL patients previously treated with high-dose MTX-based chemotherapy alone as initial treatment [104, 105]. Interestingly, the response rate was high (70%) and the median survival time from relapse was in the range of 11–16 months, quite similar to what we would expect with WBRT as initial treatment [51]. This suggests the preservation of radiation sensitivity at recurrence after high-dose MTX. Delayed neurotoxicity occurred in 15%–22% of patients, raising the question of whether or not deferred RT after high-dose MTX-based chemotherapy may reduce the risk for neurotoxicity versus that seen with immediate postchemotherapy irradiation.

Immunotherapy with Anti-CD20 Antibodies

Because most PCNSLs are neoplastic B cells expressing the CD20 surface antigen, the chimeric monoclonal antibody rituximab is a potentially active treatment for this disease. It has been successfully used in systemic DLBCLs in combination with the CHOP regimen. However, the potential efficacy of rituximab in CNS tumors when delivered i.v. is limited by its high molecular weight, which prevents its penetration into the CNS through an intact BBB. Pharmacokinetic studies have estimated that CSF levels of rituximab are approximately 0.1% of matched serum levels after i.v. administration [115]. Schulz et al. [116] re-

Table 4. Literature review: Intensive chemotherapy (ICT) with ASCT

Study	*n*	PCNSL	Induction CT	ICT–ASCT	ICT–ASCT completion	CR to ICT–ASCT	WBRT	Median follow-up (mos)	Median PFS/EFS, ASCT pts/all (mos)	OS[a] probability, ASCT patients/all	Neurotoxicity
Soussain et al. (2001) [100]	22	Recurrent/refractory	CYVE	TBC	90%	80%	No	41	–	3-yr, 60%/64%	31%
Soussain et al. (2008) [101]	43	Recurrent/refractory	CYVE	TBC	62%	96%	No	36	41/11	2-yr, 69%/45%	11%
Abrey et al. (2003) [106]	28	Newly diagnosed	MTX (3.5 g/m^2), Ara-C	BEAM	50%	57%	No	28	9/5	3 yr, 60%/NA	No
Cheng et al. (2003) [107]	7	Newly diagnosed	MTX (3.5–5 g/m^2), PCB, Ara-C	TBC	86%	100%	No	24	–	2-yr, 50%/50%	No
Colombat et al. (2006) [108]	25	Newly diagnosed	MTX (3 g/m^2), BCNU, VP16 IFO, Ara-C	BEAM	68%	76%	30 Gy	34	NR/40	4-yr, 64%/NA	No
Montemurro et al. (2007) [109]	23	Newly diagnosed	MTX (6–8 g/m^2)	Thiotepa, busulfan	69%	68%	45 Gy[b]	15	27/17	2-yr, 61%/48%	20%
Illerhaus et al. (2006) [110]	30	Newly diagnosed	MTX (8 g/m^2), Ara-C, thiotepa	Thiotepa, BCNU	77%	65%	45 Gy	63	–	5-yr, 87%/69%	17%
Illerhaus et al. (2008) [111]	13	Newly diagnosed	MTX (8 g/m^2), Ara-C, thiotepa	Thiotepa, BCNU	84%	63%	36–50 Gy[b]	25	NR	3-yr, NA/77%	No

[a] PFS and OS of patients receiving ICT–ASCT.
[b] Only in non-CR patients after ICT–ASCT.
Abbreviations: Ara-C, cytarabine; ASCT, autologous stem cell transplantation; BEAM, BCNU, etoposide, Ara-C, melphalan; CR, complete response; CT, chemotherapy; CTX, cyclophosphamide; CYVE high-dose Ara-C plus etoposide; EFS, event-free survival; IFO, ifosfamide; NA, not available; NR, not reached; OS, overall survival; PCB, procarbazine; PCNSL, primary central nervous system lymphoma; PFS, progression-free survival; TBC, thiotepa, busulfan, CTX; WBRT, whole-brain radiotherapy.

ported their experience using direct intraventricular/intrathecal administration of rituximab (10–40 mg), allowing them to reach a higher continuous concentration in the CSF, in a series of six patients. The only relevant toxicity was acute reversible paraparesia associated with back pain related to a rapid tumor cell lysis in the CSF. An objective response was observed in all four patients with leptomeningeal disease, whereas no response was obtained in the two patients suffering from a parenchymal tumor mass. Rubenstein et al. [117] conducted a phase I study in recurrent CNS lymphoma and found that intraventricular rituximab monotherapy (10–25 mg) was feasible and effective. They reported a cytologic response in six of nine patients with lymphomatous meningitis. Interestingly two of the three patients with concurrent intraocular lymphoma and one of the five patients with brain parenchymal lymphoma exhibited an objective response. These preliminary results suggest that intraventricular/intrathecal rituximab can be safely delivered and may have a role in the management of leptomeningeal and ocular disease, rather than in parenchymal tumors of PCNSL.

Intravenous rituximab has been used only in combination with a high-dose MTX-based chemotherapy regimen (MTX–procarbazine–vincristine–Ara-C, MPVA) as initial treatment before WBRT for newly diagnosed PCNSL patients [67] and with temozolomide as salvage treatment for recurrent parenchymal CNS lymphomas [118, 119]. Both combinations were associated with a high rate of response and were well tolerated, except for a higher rate of neutropenia seen when rituximab was added to MPVA. However, given the fact that the CNS penetration is poor and that the specific contribution of i.v. rituximab to these results is not evaluable, the interest in adding rituximab to chemotherapy in the treatment of PCNSL patients remains speculative. Targeting CD20 for selective radioimmunotherapy is another approach that was shown to be feasible in a pilot study including refractory or recurrent PCNSL patients using i.v. radiolabeled indium-111 and ytrium-90 anti-CD20 monoclonal antibody (ibritumomab tiuxetan) [120].

Primary Intraocular Lymphoma

Ocular involvement of PCNSL may precede clinically detectable disease in the brain and is called primary intraocular lymphoma (PIOL). The optimal treatment has not yet been defined. Because approximately 80% of patients with PIOL subsequently develop brain lymphoma, the goal of treatment should not only be to eradicate disease in the eye but also to prevent spread to the brain and the CSF. However, available data are scarce and based only on retrospec-

tive studies. In a single-center experience, Hormigo et al. [121] suggested that patients whose ocular disease was identified and treated before CNS progression had a significantly longer survival time than those who were treated only after CNS disease was diagnosed. Treatment may be focal, including ocular RT and intraocular MTX chemotherapy, or extensive, including systemic chemotherapy and WBRT. Although a recent retrospective multicenter study of PIOL patients failed to show any difference between focal and extensive therapy in terms of relapse and survival [122], most authors consider that the initial treatment of PIOL should not differ from that of PCNSL as previously described above, including high-dose MTX-based polychemotherapy and WBRT.

Conclusions

The prognosis for PCNSL patients has improved considerably over the past two decades. Currently, appropriate treatment of PCNSL can lead to prolonged remission, frequently with remarkable patient recovery compatible with an active life. A minority of patients can even hope to be cured. Long-term survivors are at a higher risk for developing severe delayed cognitive dysfunctions that may seriously compromise their quality of life. Future treatment should therefore improve efficacy while minimizing the risk for neurotoxicity. In the elderly (>60 years old), there is growing evidence to propose a chemotherapy-alone approach with a less toxic regimen and to defer or avoid RT. In younger patients, the main questions addressed in clinical trials should focus on defining the optimal chemotherapy regimen, the role of RT as consolidation treatment in complete responders to chemotherapy, and the role of ICT with ASCT as part of primary treatment. Prospective standardized neuropsychological testing is warranted. Hence, whenever possible, patients suffering from PCNSL should be referred to major centers for treatment in order to increase accrual into clinical trials and facilitate international collaborations. There is also literature suggesting that patients treated in centers with more experience do better than those treated in centers with less experience [63]. New strategies will not only benefit from advances in the management of NHL outside the CNS but also from a better understanding of specific PCNSL tumorigenesis.

Author Contributions

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