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Expert Opinion

Treatment approaches for primary CNS lymphomas

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Importance of the field: Primary central nervous system lymphomas (PCNSL) are rare but potentially curable tumours. The overall outcome for PCNSL patients is unsatisfactory and several therapeutic questions remain open. Modest progress in outcome reflects difficulties in conducting randomized trials and scarce molecular and biological knowledge.

Areas covered in this review: This review describes conventional and investigational treatments for PCNSL and focuses on the main questions for future clinical trials. PubMed and the authors' own files were utilized for references search. The terms 'PCNSL', 'primary AND CNS lymphoma', and 'CNS AND lymphoma' were used for PubMed queries. All papers published in English before November 2009 were considered.

What the reader will gain: This review illustrates how the paradigm for PCNSL treatment changed during the 1990s from radiotherapy alone to the establishment of high-dose methotrexate–cytarabine combination as standard approach. We present promising data from Phase II studies and discuss questions for randomized trials. Finally, we offer a 5-year scenario for the management of PCNSL.

Take-home message: The methotrexate–cytarabine combination should currently be considered as the reference treatment for PCNSL. Well-designed randomized trials and biological studies deriving from the use of novel technologies will be crucial to further improve outcome in these patients.

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1. Introduction

Primary central nervous system lymphomas (PCNSL) are rare, aggressive malignancies with peculiar clinical and biological features (**Box 1** and **Box 2**). They represent 4% of intracranial neoplasms and 4 – 6% of extra-nodal lymphomas. The progressive increase in incidence observed in the last decades, and the difficulties obtaining the same promising results observed in systemic lymphomas, constitute a relevant challenge. The prognosis of untreated PCNSL patients is poor and their median survival is 1.5 – 3.3 months [1]. Like their systemic counterpart, most PCNSL are sensitive to corticosteroids, chemotherapy and radiotherapy and durable, complete remissions are nowadays possible with these treatments. However, the outcome of PCNSL remains unsatisfactory, particularly when compared with that of patients with extra-central nervous system (CNS) lymphomas of a similar stage and histotype. Reported 5-year survival rates after conventional treatment with high-dose methotrexate (HD-MTX), either as a single agent or in combination, followed by whole-brain irradiation (WBRT) is close to 40% [2].

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Article highlights.

- Primary central nervous system lymphomas (PCNSL) are rare but potentially curable malignancies; overall outcome is still poor.
- Given the rarity of the disease and the patient condition at disease onset, which is often poor, it is difficult to conduct large, prospective trials in this disease; the level of clinical evidence is still low.
- A randomized trial with a complete accrual was recently successfully concluded. This suggests that upfront treatment should include chemotherapy based on the combination of high-dose methotrexate (HD-MTX) and high-dose cytarabine (HD-AraC).
- A strong commitment to enrolling patients in multicentric clinical trials, together with a consensus on crucial questions to be addressed for improving PCNSL therapies, can successfully overcome the difficulties related to disease epidemiology. Obtaining data from randomized trial in PCNSL is now an achievable goal.
- There are still many questions as to the best treatment for PCNSL. Among those we believe to be relevant are: i) the possible benefit deriving from the addition of a third chemotherapeutic agent and/or rituximab to HD-MTX/HD-AraC; and ii) the role of high-dose chemotherapy/autologous stem cell transplantation (HDC/ASCT) as a consolidation.
- Randomized trials based on the results of Phase I – II studies and a strong biological rationale should be encouraged among enlarged cooperative groups.

This box summarises key points contained in the article.

Several factors impair the development of efficacious treatments for PCNSL: i) combination chemotherapy regimens used for the treatment of systemic lymphomas have mostly proven ineffective in PCNSL because of poor drug penetration into the CNS as a result of their limited ability to cross the blood–brain barrier; ii) age, co-morbidities and/or performance status (PS) of the patients are often worse in PCNSLs than in systemic lymphomas; iii) the rarity of the disease and the poor PS of patients hampers the conduction of randomized trials; iv) the assessment of new first-line chemotherapy combinations in non-randomized trials, with divergent study designs and entry criteria, does not allow proper comparisons between different regimens.

The present therapeutic knowledge of PCNSLs results from one randomized Phase II trial with completed accrual (a prematurely interrupted randomized Phase III trial has been previously reported), single-group Phase II trials, a few meta-analyses and some large retrospective studies [2-4]. Thus, the level of scientific evidence supporting the therapeutic choices in this disease is very low and different opinions on many therapeutic aspects result in no consensus about the overall strategy and the main endpoints to be investigated in a randomized setting [4,5].

Despite several questions regarding the optimum therapeutic management of PCNSL remain open, data coming from Phase II trials have suggested the efficacy of various treatment strategies. Effective chemotherapy regimens have been developed to incorporate HD-MTX, WBRT and, more recently, high-dose cytarabine (HD-AraC).

Data from a recently reported, international, randomized Phase II trial suggest that the combination of HD-MTX and HD-AraC followed by WBRT should replace HD-MTX alone as standard chemotherapy approach for patients aged ≤ 75 years old with PCNSL. This combination should be the new control arm for a future randomized trial, as it is supported by the highest level of evidence in this field [4]. The role of other drugs (e.g., thiotepa, ifosfamide, temozolomide), monoclonal antibodies (e.g., rituximab) and high-dose chemotherapy supported by autologous stem cell transplantation (HDC + ASCT) is emerging as part of the new programmes based on the HD-MTX/HD-AraC combination; the need for consolidation of WBRT is increasingly questioned.

This review discusses the current therapeutic options in the management of PCNSL starting from an historical perspective and focusing on the rationale for the development of the future therapeutic programmes.

2. Upfront treatment for PCNSL

2.1 Radiotherapy

Historically, WBRT alone was the standard treatment for PCNSL, producing a response rate of 60 – 97%, a median survival of 14 months, a 5-year survival of 3 – 26%, and a significant improvement in neurological symptoms, performance status (PS) and quality of life [6].

However, clinical benefit obtained with upfront radiation therapy is usually transient; almost all patients treated with radiotherapy (RT) alone experience disease relapse after a few months. Relapse is local in 93% of cases, even within the RT field. A study of the Radiation Therapy Oncology Group (RTOG) has demonstrated that RT alone is unable to achieve local disease control even with higher radiation doses [6,7]. Additionally, hyper-fractionation and accelerated RT do not improve survival, and increase treatment-related toxicity [6,7]. However, despite the disappointing outcome previously reported with RT as an exclusive treatment, this strategy remains a valid alternative for elderly patients with organ dysfunction or patients with poor PS who are ineligible for chemotherapy.

The addition of chemotherapy to RT has been recommended to improve survival of PCNSL patients. Three large, retrospective, multicentre surveys reporting therapeutic results in over 1000 patients treated in Europe and Japan suggest the superiority of the combined strategy [8-10]. These studies uniformly showed that HD-MTX (≥ 1 g/m^2) is the most efficient known cytostatic; whereas any regimen without HD-MTX is associated with outcomes similar to RT alone [11,12].

Although a survival advantage for HD-MTX-based chemotherapy followed by RT has not been fully proven, a

Box 1. Biology of PCNSL in immunocompetent patients.

Mostly Epstein–Barr-virus (EBV)-negative, diffuse large B-cell lymphomas in immunocompetent patients. Tumour cells seem to be derived from a germinal centre exit B cell. Notably, most PCNSL in HIV-infected patients in the pre-HAART (highly active anti-retroviral activity) era were EBV associated.

Chromosomal translocations, gains and losses of genetic material, ongoing aberrant somatic hypermutation (SHM), tumour suppressor genes mutations, gene inactivation by DNA methylation and NF-κB activation are events implicated in transformation.

Analysis of site-specific genomic aberrations suggests that two major groups of genes – one involved in the immune response, including regulation of HLA expression, and the other involved in apoptosis, including the p53 pathway – could be implicated in PCNSL pathogenesis

The existence of specific interactions between PCNSL cells and the CNS microenvironment has been postulated given the selective manifestation of PCNSL in the CNS and the observation that extra-cerebral relapses are extremely rare. However, it is not yet known whether B cells enter the CNS as non-malignant or malignant B cells.

CD4 and CD8 T cells, non-malignant B cells, and macrophages/microglia are often involved in the characteristic infiltrate of these tumours. It has been suggested that the tumour cells of PCNSL might down-regulate the intracerebral immune response by anti-inflammatory cytokines such as interleukin (IL)-4 and IL-10, and thus may escape immune surveillance. The high frequency of human leucocyte antigen (HLA) loss reported in these tumours supports this hypothesis.

A preferential usage of the *IGHV4 – 34* gene segment has been reported in these tumours. Nevertheless, there is no clear evidence in favour of an antigen-driven proliferation for these tumours.

Box 2. Epidemiology and clinical presentation of PCNSL.

Rare form of extra-nodal B cell neoplasm that accounts for 4% of all primary brain tumours.

Propensity for elderly populations with a median age at diagnosis of 60 years.

Patients typically present with symptoms that are suggestive of focal neurologic dysfunction that depend on the location of the tumour.

Common symptoms and signs include: i) cognitive, behavioural, and personality changes; ii) headaches, hydrocephalus or other signs of increased intracranial pressure; and iii) acute onset of weakness, aphasia, or sensory disturbances. Seizures are uncommon.

Prognostic factors include: i) age; ii) Eastern Cooperative Oncology Group performance status; iii) serum lactate dehydrogenase level; iv) cerebrospinal fluid (CSF) protein level; and v) tumour location. These five parameters together compose the elements of a prognostic score, confirmed by the International Extranodal Lymphoma Study Group (IELSG), which divides patients into three risk groups.

Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain tends to demonstrate a supratentorial mass that is commonly deep or peri-ventricular in location. The most common locations are the cerebral hemispheres, basal ganglia and corpus callosum.

On MRI, PCNSL are usually hypo-intense on T1 images and hypo- to iso-intense on T2 images. Contrast enhancement is diffuse and relatively homogeneous.

randomized trial comparing this strategy with RT alone is unlikely to be acceptable to the majority of clinicians, and the combined approach should be retained as the first-choice strategy for patients with PCNSL [11,12]. As a consequence, the role of RT has been progressively changed from exclusive strategy to post-chemotherapy consolidation.

There is a general consensus that PCNSL is a multifocal disease, even when unproven by conventional neuroimaging. In effect, PCNSL seems to infiltrate CNS areas distant from those detected by MRI, as suggested by autopsy studies. Thus, prospective trials addressing new chemoradiation combinations against PCNSL currently foresee the irradiation of the whole encephalon, with variable ranges of doses. A single retrospective Japanese series focused on the role of partial-brain irradiation showed similar cumulative in-field and out-field recurrence rates at 5 years according to the extension of field margins (≥ 4 vs < 4 cm) [13]. This study showed a significantly lower out-field recurrence rate (22 and 83%; p = 0.0079) and a trend towards significantly better survival for patients treated with margins of ≥ 4 cm with respect to patients irradiated with margins < 4 cm [13]. However, these intriguing exploratory results cannot be applied to the general PCNSL population as most Japanese patients had worse prognostic factors; a wide radiation dose range was therefore used and only 14% of patients were treated with HD-MTX-based chemotherapy [13]. Even if primary chemotherapy followed by partial brain irradiation represents an intriguing approach that warrants further investigation, standard radiation treatment for PCNSL patients should currently include the whole brain.

Following the further progress with combination chemotherapy regimens and the consequent increase in proportion of long-term survivors, late neurotoxic effects of consolidation WBRT became increasingly evident. These varying effects can include treatment-related dementia, gait disturbance and

urinary incontinence. Patients > 60 years of age and those who receive HD-MTX and/or intrathecal chemotherapy seem to have an increased risk [14]. As a result, and with the aim of reducing the risk of treatment-related neurotoxicity, recent studies and clinical practice guidelines have chosen to defer or avoid WBRT in patients who achieve a complete response with initial chemotherapy. In some preliminary but interesting trials, a significantly reduced radiation dose has been used in PCNSL patients with good neurotolerance and without apparent survival impairment. At our institution, WBRT doses ≥ 40 Gy and tumour bed doses ≥ 45 Gy were not associated with a better local control or survival in PCNSL patients in complete remission (CR) after HD-MTX-based chemotherapy. These observations are consistent with those of a large prospective trial [7], showing that two different consolidation strategies – a conventional 45 Gy WBRT and a 36 Gy hyperfractionated WBRT – were associated with similar progression-free survival (PFS). The observations are also consistent with the results of a single-arm Phase II trial [15], in which WBRT dose reduction to 23.4 Gy in patients in CR after primary chemotherapy yielded a 2-year overall survival (OS) of 89%, which is over imposable to results obtained with a similar chemotherapy but followed by WBRT 45 Gy [16]. In these series, neurological impairment was strongly associated with the WBRT dose, with a progressive decline in the results of the Mini-Mental State Examination (MMSE) and detection of bradipsychia, memory deterioration and dysphasia in patients irradiated with > 36 Gy. WBRT with 45 Gy has been associated with delayed neurotoxicity in 25% of cases, which reached 83% among elderly patients [7], whereas a consolidation WBRT dose of 23.4 Gy was not associated with neurocognitive decline [15]. In fact, the systematic use of a complete battery of neuropsychological tests in the latter prospective trial showed no significant cognitive decline up to 24 months of follow-up, although it detected some difficulties in verbal memory and motor speed persisting over this follow-up period. All together, these observations seem to suggest that the consolidation WBRT dose can be consistently reduced without impairing survival results but improving the neurotoxicity profile, and constitutes the background for future randomized trials addressing the role of consolidation low-dose WBRT in PCNSL patients.

2.2 Chemotherapy

Three major subgroups of drugs are classified according to their capability to cross the blood–brain barrier (BBB). First, there are drugs with a very low capability to cross the BBB, which can be administered at very much higher doses than other drugs to obtain therapeutic concentrations in the tumour tissue and lymphoma-surrounding neural tissue; for example, MTX and AraC. Second, are drugs with a very low capability to cross the BBB that cannot be administered at high doses because they are associated with relevant dose-limiting toxicity. This is the case of anthracyclines, vinca alkaloids and some alkylating agents, which represent the backbone of treatment of extra-CNS lymphomas but exhibit negligible activity in PCNSL. Third, are those chemotherapeutic agents able to cross the BBB and to reach therapeutic concentrations in the tumour bed. This is the case of thiotepa, ifosfamide, temozolomide, and nitrosoureas, among others, which are frequently included in chemotherapy combinations for PCNSL, both in experimental trials and ordinary clinical practice.

2.2.1 *The CHOP regimen*

Standard chemotherapy for systemic lymphomas has been proved to be poorly effective in PCNSL. Although regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) may induce an initial radiological response in PCNSL, these responses are not durable and patients relapse rapidly. In a randomized trial, which did not reach the expected accrual (n = 53), Mead *et al.* evaluated WBRT versus WBRT and CHOP regimen. The FFS rate at 12 months was 59% in the WBRT group and 42% in the RT-CHOP group [3]. In another prospective study of 31 patients treated with more intensive chemotherapy (13 shortened MACOP-B [cyclophosphamide, doxorubicin, vincristine, bleomicine, methotrexate, prednisone] and 18 modified MACOP [cyclophosphamide, doxorubicin, vincristine, prednisone] with HD-MTX followed by WBRT), CR rate after chemotherapy and radiotherapy was 69% and after a median follow-up of 24 months median survival was 23 months with an actuarial 5-year survival of 34%. The addition of CHOP or other anthracycline-containing regimens to HD-MTX produces results similar to those of HD-MTX alone, with a CR ranging from 60 to 67% and a median OS of 20 – 25 months. Meanwhile, an increased toxicity is reported with these regimens [17,18].

As a result of the apparent lack of benefit and of scientific evidence supporting their use, and to the increased risk of toxicity, the CHOP and CHOP-like regimens have been abandoned in PCNSL.

2.2.2 *High-dose methotrexate*

In the early 1980s, it was observed that patients with systemic lymphoma who had CNS relapse responded to HD-MTX. This observation drew attention to this drug as a potentially active treatment for PCNSL. MTX is a folate antagonist with a poor CNS penetration when administered at standard doses (< 100 mg/m^2). The administration of doses from 1 to 8 g/m^2 has been proved to be feasible and relatively safe [7,14,17,16,19-34,15]. Rapid infusion of 3 g/m^2 of MTX over 3 h has been demonstrated to achieve cytocidal (1 µmol/L) concentrations of the drug in the cerebrospinal fluid (CSF), whereas patients treated with < 3 g/m^2 do not reliably achieve these cytocidal concentrations of MTX in the CSF.

Three different MTX doses have been used in clinical trials assessing activity of single-agent HD-MTX in patients with PCNSL (**Table 1**): two trials with MTX 8 g/m^2 every 2 weeks deferring WBRT until failure [19,24], two trials with MTX 1 g/m^2 immediately before WBRT [14,30] and two trials

Table 1. Published prospective trials on PCNSL in immunocompetent patients treated with chemotherapy alone or combined treatment.

Ref.	N°	TS*	Primary Chemotherapy‡			ORR§	CRR¶	Median follow-up	OS		Neuro toxicity
			Drugs	M dose	it CHT				2-years	5-years	
Series treated with CHT alone											
[28]	31	C	M	8 g/m^2/14 d	-	100%		31 mo.	63%	NR	0%
[20]	50	C	M L P MP	1 g/m^2/10 d	M	48%	42%	36 mo.	45%	NR	8%
[19]	25	C	M	8 g/m^2/14 d	-	74%	52%	23 mo.	70%	NR	5%
[25]	65	C	M V I C A	5 g/m^2/28 d	ivM/a	71%	61%	26 mo.	69%	43%	3%
[24]	37	C	M	8 g/m^2/14 d	-	35%	30%	56 mo.	51%	25%	20%
Series treated with HD-MTX plus RT											
[29]	25	CR	M	3.5 g/m^2/21 d	-	88-92%	56%-88%	60 mo.	58%	38%	8%
[30]	46	CR	M	1 g/m^2/7 d	a*	NR - 95%	NR - 82%	36 mo.	62%	37%	22%#
[14]	31	CRC	M	1 g/m^2/7 d	M	64-87%	NR - 87%	97 mo.	72%	22%	32%
Series treated with HD-MTX-containing CHT plus RT											
[31]	25	CR	A a C M O P	3 g/m^2/21 d	M/a/P	72 – 72%	67%-78%	24 mo.	70%	56%	0%
[17]	57	CRC	a Bn M O ± CHOP	1.5 – 3 g/m^2/14 d	-	68 – 71%	62%-64%	59 mo.	60%	36%	NS
[32]	56	CR	Bn M N P	1.5 g/m^2/28 d	M	71% – 100%	54%-61%	8 mo.	86%	NS	29%
[33]	31	CR	A B C M O P	2 g/m^2/15 d	M/a/P*	89 – 67%		24 mo.	48%	36%	7%
[16]	52	CRC	M N O	3.5 g/m^2/7 d	M	90 – 94%	56%-87%	60 mo.	75%	40%	25%
[7]	102	CR	M N O	2.5 g/m^2/14 d	M	94 – NR	58%- NR	56 mo.	64%	32%	15%
[26]	52	CR	Bn M O P	3 g/m^2/14 d	M	NR – 81%	33%-69%	27 mo.	69%	NR	12%
[34]	41	CR	A I M T	3.5 g/m^2/21 d	-	76 – 83%	44%-56%	49 mo.	50%	41%	NR
[15]	30	CRC	M N O R	3.5 g/m^2/14 d	M*	93%-NR	44%-77%	37 mo.	67%	NR	NR

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Only trials on 25 patients or more and published as original articles are considered. Trials on high-dose chemotherapy supported by autologous stem cell transplant are excluded. N: Number of enrolled patients.

*Treatment sequence: C: Chemotherapy alone; CR: Chemotherapy followed by radiotherapy; CRC: Chemotherapy followed by radiotherapy and further chemotherapy.

‡Primary chemotherapy: A or H: Adriamycin; a: Cytarabine; B: Bleomycin; Bn: BCNU; C: Cyclophosphamide; Cn: CCNU; E: Etoposide; M: Methotrexate; m: Nitrogen mustard; N: Procarbazine; O: Vincristine; P: Prednisone or other corticoids; R: Rituximab; T: Thiotepa; V: Teniposide. Series using intrathecal chemotherapy (it CHT) exclusively in patients with positive CSF cytology at diagnosis are marked with an asterisk.

§ORR: Overall response rate; in series treated with combined modality, response rate after chemotherapy and (-) after the entire planned treatment is reported.

¶CRR: Complete remission rate; in series treated with combined modality, response rate after chemotherapy and (-) after the entire planned treatment is reported.

NS: not specified; NR: not reported. # 5-year risk rate.

with MTX 3.5 g/m^2 every 3 weeks followed by WBRT [4,29]. HD-MTX at 8 g/m^2 yielded an apparently different overall response rate (ORR) in Europe and the USA (51% for the German trial and 68% for the American trial), but a super imposable 3-year OS rate of 33 – 35% [19,24], which is similar to the 3-year OS of 32 – 47% recorded in the 3.5 g/m^2 trials [4,29]. Noteworthy in the trials using MTX 8 g/m^2, dose reduction due to impaired creatinine clearance was indicated in 45% of patients, whereas in the 3.5 g/m^2 trials only a few patients needed a reduction in MTX dose. Response to the drug has not been assessed in trials using MTX 1 g/m^2 immediately before WBRT, whereas the 3-year PFS and OS were 47 – 50% and 45 – 50%, respectively [14,30]. Thus, although it is not possible to exclude higher doses or different administration schedules of this drug from improving outcome, tolerability and activity data from 3.5 g/m^2 trials are very similar to those reported with higher MTX doses. This observation suggests that this dose level could be a good compromise for safety, feasibility and efficacy and should be used as reference dose for combination regimens.

2.2.3 *Methotrexate-based multi-drug regimens*

Attempts to improve the outcome of HD-MTX results include the addition of other drugs to HD-MTX and the use of strategies to improve the delivery of this and other drugs into the CNS. A combination of MTX, procarbazine and vincristine (MPV) has been proposed on an empirical basis, given the observation that these three drugs have different mechanisms of action, different toxicity profiles and might be active inside the CNS. Vincristine does not cross the intact BBB but, when the BBB is disrupted by a tumour, this drug seems to reach areas of bulky disease [35]. Procarbazine is an oral lipophilic alkylating drug that can cross the BBB. The RTOG/SWOG 93 – 10 study used this three-drug regimen, followed by WBRT and two cycles of HD-AraC. After a median follow up of 56 months, a 2- and a 5-year OS respectively of 64 and 32%, respectively, was reported, with a 15% incidence of neurotoxicity [7].

The rationale for the administration of HD-AraC after HD-MTX is the continuance of the exposure of proliferating cells to S-phase cytostatics and the increase of cytarabine-cytidine triphosphate formation and DNA incorporation, with a consequent increased cytotoxicity. Different combinations based on MTX and AraC have been used in patients with PCNSL, mostly with promising results. Findings from a meta-analysis of 19 prospective trials of PCNSL [36] and an international retrospective study of 378 patients [8] suggested a survival improvement resulting from the addition of HD-AraC to HD-MTX.

Based on this rationale, the IELSG #20 trial [4] – the first randomized Phase II trial with completed accrual on the primary chemotherapy in PCNSL – was designed. In this study, 79 patients with newly diagnosed PCNSL were randomly assigned to receive four cycles of HD-MTX (3.5 g/m^2) on day 1, every 21 days, alone (control arm) or in combination with AraC 2 g/m^2, twice a day, on days 2 and 3 (experimental arm). Chemotherapy was followed by WBRT. Despite the expected increase in the toxicity profile (almost exclusively haematological), the addition of AraC to MTX has been associated with an increased complete remission rate (the primary endpoint), from 18 to 46% ($p = 0.006$). Additionally, the overall response rate has been significantly improved in the combination group (43 vs 69%, $p = 0.009$), and, at a median follow-up of 30 months, the combination of HD-MTX and HD-AraC has been associated with significantly better event-free and OS with respect to HD-MTX alone. Thus, this randomized trial has clearly documented an advantage to associating HD-AraC and HD-MTX, over HD-MTX alone.

Given the sensitivity of lymphoma cells to high-dose steroids, these drugs have also been evaluated in combination with HD-MTX. In a trial conducted on behalf of the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group [26], 52 patients were treated with a combination of MTX, teniposide, carmustine and methylprednisolone plus intrathecal chemotherapy and subsequent WBRT. Overall response rate was 81% and the 2- and 3-year survival rates were 69 and 58%, respectively. Notably, five (10%) patients died, probably because of infectious complications. It should be taken into account that most PCNSL patients receive prolonged steroid therapy to treat perilesion oedema and related symptoms. The real benefit of the addition of steroids to HD-MTX-based chemotherapy remains undefined, whereas there are several concerns about the possible immunosuppressive effects of prolonged steroid therapies.

Thiotepa is another lipophilic agent potentially useful in PCNSL. This drug has been combined with HD-MTX, HD-AraC and idarubicin (MATILDE regimen) [34] followed by WBRT, and assessed in a non-randomized Phase II trial on 41 patients. This regimen resulted in an overall response rate of 83% and a 5-year OS of 41%. Due to its properties, thiotepa has been included in high-dose sequential chemotherapy programmes followed by autologous transplantation both as part of the pre-harvest phase and of the conditioning regimens (see below).

Patients older than 60 years represent about 50% of PCNSL patients and exhibit an increased risk of complications. In this epidemiologically relevant setting, the use of drugs with a good safety profile, in particular, with reduced haematological toxicity, deserves to be further investigated. For instance, a single-arm Phase II study has demonstrated that the combination of MTX and temozolomide is feasible and is associated with some durable responses. Temozolomide, an oral alkylating agent, is a suitable candidate for combination therapies because it permeates the BBB, has *in vitro* additive cytotoxic activity with radiotherapy [37] and shows only mild toxicity.

2.3 High-dose chemotherapy supported by autologous stem cell transplantation

The combination of HDC/ASCT has been proposed as a therapeutic option to improve outcome in selected patients with PCNSL. The rationale for the use of HDC/ASCT is multiple and includes the administration of high doses of cytostatics to overcome drug resistance and to achieve therapeutic concentrations in the lymphoma tissue and other chemotherapy sanctuaries, like CSF, meninges and eyes, where lymphoma cells usually grow. HDC/ASCT has been used in patients with relapsed or refractory PCNSL.

The first experience with HDC/ASCT began in 1992, in France, among patients with relapsed intraocular lymphoma; subsequently, it has been applied to every patient with recurrent PCNSL [38]. Twenty-two patients (median age 53 years, range 27 – 64), half with relapse limited to the eyes, have been treated with two courses of AraC–etoposide combination, and patients with chemo-sensitive lymphoma had been treated with a combination of thiotepa, busulfan and cyclophosphamide followed by ASCT. Complete remission rate after the whole treatment was 80%, with grade 4 neutropenia and thrombocytopenia in all patients, septic complications in 86% of cases, and 23% treatment-related mortality (TRM), mostly among patients older than 60 years [38]. With this strategy, the 3-year event-free survival (EFS) and OS were 53 and 64%, respectively. Importantly, 32% of patients developed severe neurologic toxicity, which was lethal in one third of affected patients. This complication, consisting of severe chronic leukoencephalopathy with cognitive dysfunction, had been equally observed both in elderly patients (≥ 60 years old, n = 7) [38] who did not receive WBRT and in previously irradiated younger patients.

These results led the same authors to conduct a second Phase II trial, always on relapsed/refractory patients, and treated with the same strategy as described before [39]. In this trial, 43 PCNSL patients were enrolled. CRR after the whole treatment was 60%, and TRM was 16%. Severe neurotoxicity has been observed in 12% of cases. After a median follow-up of 36 months, the 2-year OS was 45%. The encouraging results reported in patients with relapsed/refractory disease prompted several groups to include ASCT as part of first line PCNSL treatment.

2.3.1 *Upfront HDC/ASCT*

To date, seven trials focusing on HDC/ASCT as part of first-line treatment for PCNSL have been reported [22,40-45] (**Table 2**). These trials included induction chemotherapy, with or without intensification and followed by conditioning chemotherapy supported by ASCT, followed or not by WBRT. Induction chemotherapy included HD-MTX in all reported trials, with a dose ranging from 3 g/m^2 [40,41] to 8 g/m^2 [42-44], for a total of two to five cycles. HD-MTX has been administered as single-drug induction in five trials [22,42-45] resulting in 39% of grade 3 – 4 toxic events. CRR after induction chemotherapy has been 14 – 21% after HD-MTX alone [22,42-45] and 44% after a combination of MTX 3 g/m^2, carmustine (BCNU), etoposide and methylprednisolone (MVBP regimen), which has been used in two small series [40,41]. The low activity of MTX monochemotherapy gave rise to intensification before ASCT, whereas severe toxicity resulted in patient exclusion from HDC/ASCT, requiring WBRT.

AraC, alone [22,45] or in combination with thiotepa [42,43] or ifosfamide [40,41], has been used as mobilizing drug before conditioning and to intensify treatment after HD-MTX-based induction. Blood stem cell harvesting was efficacious in all the trials; however, intensification with AraC alone [22] or combined with thiotepa [42,43], did not further improve response rates with respect to those obtained with HD-MTX-based induction therapy [40,41].

ASCT conditioning combinations used in the treatment of PCNSL can be divided into BEAM- (BCNU 300 mg/m^2 day 7, etoposide 100 mg/m^2 every 12 h days 6 – 3, cytarabine 200 mg/m^2 every 12 h days 6 – 3, melphalan 140 mg/m^2 day 2) regimen [22,40,41] and thiotepa-based combinations (busulfan–thiotepa and BCNU–thiotepa) [42-45]. Among these combinations, busulfan–thiotepa appeared to be particularly toxic. In fact, TRM was 6 – 7% in patients treated with BEAM regimen [22,41], 0% in those treated with BCNU–thiotepa conditioning [42,43] and 13% in patients treated with a high-dose busulfan–thiotepa combination [44].

With a median follow-up of 28 – 34 months, patients treated with HD-MTX-based induction and BEAM conditioning exhibited a 4-year EFS and OS for the whole series of 15 – 46% and 60 – 64%, respectively [22,41]. These actuarial figures were obviously superior when only actually transplanted patients were considered, with a 4-year EFS and OS of 43 – 66% and 60 – 75%, respectively [22,41]. At a median follow-up of 15 months, series treated with HD-MTX-based induction and high-dose busulfan–thiotepa conditioning exhibited a 2-year EFS and OS 45% and 48% for the whole series, and 48 and 61% for transplanted patients [44]. These results have been strongly conditioned by the low activity of induction therapy and the high TRM of the programme [44]. After a median follow-up of 63 months, 67% of patients treated with BCNU–thiotepa conditioning were alive, with a 5-year OS of 69% for the whole series and 87% for patients actually treated with HDC/ASCT [42]. With the same chemotherapy schedule, but keeping WBRT only for non-responders, the 3-year disease-free survival (DFS) and OS were 77% [43]. Relapses after ASCT usually occurred within the first 2 years of follow-up, but a few cases of relapse after 5 years have been also reported [42]. Deaths in these trials were comprehensively due to primary progression (50% of deaths), relapse (38%) or toxicity (13%).

Given its ability to increase the rate of CR, WBRT has been maintained as part of the consolidation in many HDC/ASCT programmes. The addition of WBRT after these therapies and, in particular, after a sequential HD-MTX and

Table 2. Main features of reported studies on the role of HDC/ASCT in PCNSL.

Ref.	N° pts	Median age (range)	Treatment line	Therapy (induction → intensification)	ASCT conditioning	WBRT	Outcome	Neuro toxicity	Median f-up (months)	TRM
[38]	22	53 (27 – 64)	Salvage	araC + VP16	TT/Bu/Cy	No	3-y OS 64%	32%	41	4%
[39]	43	52 (23 – 65)	Salvage	araC + VP16	TT/Bu/Cy	No	2-y OS 45%	5%	36	7%
[40]	6	53 (30 – 66)	First-line	MBVP → IFO + araC	BEAM	Yes	2-y OS 40%	33%	41	0%
[41]	25	52 (21 – 60)	First-line	MBVP → IFO + araC	BEAM	Yes	4-y OS 64%	8%	34	4%
[42]	30	54 (27 – 64)	First-line	HD-MTX → araC + TT	BCNU/TT	Yes	5-y OS 69%	17%	63	3%
[43]	13	54 (38 – 67)	First-line	HD-MTX → araC + TT	BCNU/TT	Yes‡	3-y OS 77%	0%	23	0%
[44]	23	55 (18 – 69)	First-line	HD-MTX → -	Bu/TT	Yes‡	2-y OS 48%	39%	15	13%
[22]	28	53 (25 – 71)	First-line	HD-MTX → araC	BEAM	No	2-y OS 55%	0%	28	4%
[45]	7	56 (41 – 64)	First-line*	HD-MTX → araC	TT/Bu/Cy	No	3-y OS 50%	0%	28	14%

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araC: Cytarabine; ASCT: Autologous stem cell transplantation; BCNU: Carmustine; BEAM (regimen): Carmustine, etoposide, cytarabine, and melphalan; Bu: Busulfan; Cy: Cyclophosphamide; IFO: Ifosfamide; MBVP (regimen): Methotrexate, carmustine, etoposide, and methylprednisolone; OS: Overall survival; TRM: treatment-related mortality; TT: thiotepa; VP16: Etoposide; WBRT: Whole-brain irradiation.

*One patient received the treatment as salvage therapy.

‡Only for patients not achieving a complete remission.

HD-AraC/thiotepa induction followed by high-dose BCNU/thiotepa conditioning has been associated with an increased incidence of severe neurotoxicity. As a consequence, a German group proposed avoiding consolidation WBRT in patients in CR after ASCT to reduce this severe complication. In a pilot study involving 13 patients, this group obtained encouraging results (3-year DFS and OS: 77%), that deserve further investigation [43]. The benefits and side effects of these consolidative strategies (i.e., conventional WBRT and HDC/ASCT), deserve to be compared in a randomized trial to draw definitive conclusions on the role of consolidation both on efficacy and neurotoxicity in patients with newly diagnosed PCNSL. To this purpose, the IELSG 32 study (http://www.ielsg.org/trialson.html) should be mentioned. This ongoing trial compares the activity of three different chemotherapy combinations: HD-MTX + HD-AraC, HD-MTX + HD-AraC + rituximab and HD-MTX + HD-AraC + rituximab + thiotepa. Importantly, this trial will test, in a randomized design, the efficacy of two consolidation strategies: conventional WBRT versus HDC/ASCT.

2.4 Immunotherapy, chemo-immunotherapy and radio-immunotherapy

Some preliminary evidence in the PCNSL literature supports a role for rituximab, an anti-CD20 hybrid monoclonal antibody that is active against different types of B-cell lymphomas. In fact, the addition of rituximab to CHOP (R-CHOP) has significantly improved therapeutic results in patients with diffuse large B-cell lymphoma [46], the most common histological category of PCNSL. However, there are many doubts about the capability of this antibody to cross the BBB and a large, randomized trial comparing CHOP with R-CHOP did not show any role for this drug in preventing CNS dissemination [47].

In PCNSL, an ongoing study of the Eastern Cooperative Oncology Group suggests that rituximab can be active against relapsed PCNSL (T. Batchelor, personal communication). Results from a Phase II trial of 30 patients show that the addition of rituximab to a MPV chemotherapy regimen is feasible and associated with a high response rate (complete response rate 78%, overall response rate 93%), and a 2-year OS and PFS of 67 and 57%, respectively [15]. These survival data were comparable or superior to other clinical trials, including those reported with the MPV regimen; however, it is not possible to draw conclusions on the efficacy of R-MPV combination versus MPV and the precise role of rituximab in PCNSL remains to be defined, perhaps in a randomized setting. Consistent with other reports pharmacokinetic studies, this trial demonstrates that rituximab penetrates the CSF, with levels ranging from 0.1 to 4.4% of serum levels. It should be noted that the addition of rituximab to HD-MTX-based chemotherapy resulted in an increased rate of neutropenia that required growth factor support.

Pilot studies in patients with refractory disease evaluated the potential role of ibritumomab, a murine anti-CD20 antibody, which can be conjugated via a linker chelator (tiuxetan) to radioisotopes for radio-immunotherapy. This anti-CD20 conjugated with ^{90}-yttrium (^{90}Y) is currently used in relapsed follicular lymphomas and it is being investigated in other B-cell lymphomas. ^{90}Y-ibritumomab tiuxetan has been tested in two small PCNSL series, suggesting that this approach is feasible in patients with PCNSL and providing evidence of brain lymphoma targeting, which suggests that these radioimmunotherapies could be delivered as a component of PCNSL treatment [48]. Unfortunately, preliminary data show that ^{90}Y-ibritumomab tiuxetan is less active in these malignancies, with some interesting cases of progressive disease in CNS sites distant from the primarily involved areas. This feature

suggests that this radio-immunoconjugate is unable to adequately treat microscopic lesions with the intact BBB.

2.5 Strategies to improve drug bioavailability in the CNS parenchyma

Intracarotid infusion with disruption of the BBB has been used in an effort to improve the delivery of cytostatics into the CNS. This approach involves cannulation of the carotid or vertebral arteries under general anaesthesia, osmotic disruption of the BBB with mannitol infusion, and intra-arterial chemotherapy. This strategy has been used successfully without the need for WBRT, with a 68% response rate and a median OS of 41 months; however, it seems to be less active than other standard intravenous chemotherapy combinations followed by WBRT, and a plateau in the survival curve has not been achieved [49]. Moreover, the requirement of general anaesthesia and of an invasive procedure on CNS arteries in patients who are often much compromised raises some concerns on the effective feasibility of this procedure outside highly specialized centres.

2.5.1 Strategies to improve drug bioavailability in sanctuaries

The meningeal spaces and vitreal humors are two areas where bioavailability of cytostatics is extremely variable and conditioned by pharmacokinetics that are not well understood. These areas are usually described as chemotherapy sanctuaries. To overcome these limitations, some investigators suggested delivering cytostatics into these areas by direct injection, that is by intrathecal, intraventricular or intravitreal routes. The efficacy and tolerability of these strategies in patients with PCNSL have not been still assessed as primary endpoints of well-designed prospective trials.

Although randomized studies are lacking, intrathecal chemotherapy has long been used as part of treatment in PCNSL. The advent of HD-MTX-based regimens made the use of intrathecal treatment controversial, in particular for patients who receive at least 3 g/m^2 of MTX. This dose level results in therapeutic MTX concentrations (10 μM) in the CSF and increased rates of cytological complete remission, while lower doses resulted in unpredictable levels [50]. Intrathecal administration produces drug levels 10-fold higher than those obtained with systemic chemotherapy [51]. MTX, cytarabine and steroids are the drugs most commonly delivered by the intrathecal route, mostly using an intraventricular Ommaya's reservoir, which affords more reliable CSF distribution than lumbar injection. A sustained-release formulation of cytarabine (liposomal cytarabine) for intrathecal injection is available and allows dosing once every 14 days.

Intrathecal chemotherapy is associated with increased risks of neurotoxicity and chemical meningitis, whereas its efficacy in PCNSL patients has not been prospectively assessed. Even if only a minority of relapsed patients are routinely assessed for meningeal recurrence, the majority of meningeal relapses seems to occur in patients with positive CSF cytology at diagnosis [8,18,29]. This has led some authorities to suggest that, to minimize toxicity, intrathecal chemotherapy should be reserved for patients with positive CSF cytology [29,52]. However, this recommendation could result in undertreatment, as CSF cytology examination is associated with a finite false-negative rate [53,54].

With regard to Phase II studies with HD-MTX, intrathecal chemotherapy with MTX, cytarabine and steroids has been used in all patients, regardless of CSF cytology status, in two studies [2]. No adverse events have been reported. CSF and meningeal relapses have not been reported in series treated with intrathecal chemotherapy, whereas they constituted 11% of all relapses in one of the series treated without this strategy [2]. Conversely, some prospective [18,29,55] and retrospective [8,56] studies suggest that intrathecal chemotherapy does not improve outcome in patients who receive HD-MTX-based chemotherapy. Moreover, preliminary data suggest that systemic HD-MTX is associated with eradication of neoplastic cells from CSF [28,57], which deserves to be confirmed in future trials.

The intrathecal route has been explored to delivery rituximab inside the CNS. Pharmacokinetic analysis in monkeys suggests that drug clearance from the CSF is biphasic, with a terminal half-life of 4.96 h [58]. No significant acute or delayed toxicity was detected after intrathecal rituximab delivery. Responses were recorded in several case reports and a small Phase I trial [59]. Doses up to 25 mg, administered twice a week by Ommaya's reservoir, were safely delivered, while a dose of 50 mg has been associated with nausea, vomiting, arterial hypertension, diplopia and tachypnoea. Objective responses have been achieved in half of the patients treated, but have been followed by early cytological failure or cerebral progression [59]. Thus, intraventricular rituximab can be safely administered in patients with CNS lymphoma, but its efficacy should be further demonstrated.

Intraocular lymphoma is a subset of PCNSL in which malignant lymphoid cells invade the retina, vitreous body, or optic nerve head. Although a common proposed approach includes combination of HD-MTX-based chemotherapy and radiotherapy, a standard treatment does not exist yet. In a small series of PCNSL patients, micromolar concentrations of MTX were achieved in the aqueous and vitreous humor when the drug was given at a dose of 8 g/m^2. However, intraocular drug concentrations were erratic, were not predictive of response and were lower in the vitreous humor, where lymphomatous cells usually grow, than in the aqueous humor [60]. As a consequence of these difficulties to achieve therapeutic drug concentrations into the eyes, ocular failure is common. Good rates of ocular disease control combining ocular irradiation to MTX-based chemotherapy have been reported [61,62]. Promising results seem to derive from the intraocular administration of methotrexate by injections [63,64]. In a series of 16 patients with intraocular lymphoma, intravitreal MTX (400 μg/0.1 mL) has been associated with a clinical clearance

of malignant cells in all cases, after a maximum of 12 MTX injections. A second remission was induced in three patients, who have been treated with a further course of intravitreal chemotherapy after their tumour recurred within the eye. The most commonly observed complications were cataract, corneal epitheliopathy, maculopathy, vitreous haemorrhage, optic atrophy, and sterile endo-ophthalmitis. No patient had irreversible loss of vision that could be definitely attributed to the intravitreal injection of MTX. Thus, intravitreal chemotherapy with MTX is effective in inducing clinical remission of intraocular tumour in PCNSL with acceptable morbidity.

3. Relapsed and refractory PCNSL

About 50% of newly diagnosed PCNSL patients will develop recurrent or refractory disease, thus needing a salvage treatment. A few data on the optimum approach to management in this setting are available and the level of clinical evidence relies on Phase I – II trials enrolling a limited number of patients. Moreover, treatments for relapsed or refractory disease are frequently limited by patients' performance status and therapeutic toxicity. The selection of treatments for recurrent disease is thus individualized on the basis of both tumour-related and patient-related characteristics. Treatment options at the time of tumour progression are mostly determined by the treatment given at diagnosis and by the timing of tumour progression (**Table 3**).

Patients treated without WBRT as part of first-line treatment can be effectively treated with WBRT at a later stage, although the risk of treatment-related neurotoxicity is a concern [65,66].

In patients who received HD-MTX re-induction, the same regimen can be successful if a reasonable time interval has elapsed from initial MTX-based treatment. Re-treatment with HD-MTX has been associated with 92% ORR, median PFS of 26 months and 1-year OS of 70%, but it has been used in a selected group of patients who had experienced durable response to upfront HD-MTX based chemotherapy.

A few salvage combinations have been designed to include PCNSL active drugs other than MTX. For example, salvage poly-chemotherapy with etoposide (VP-16), ifosfamide and AraC has been associated with 37% ORR, median PFS of 5 months and 1-year OS of 41% [67].

Mono-chemotherapy with temozolomide is an active treatment for patients with relapsed or refractory PCNSL [37]. In clinical practice, its favourable tolerability profile makes this drug a valid option also for elderly and frail patients. More recently, a combination of temozolamide and rituximab was proposed and evaluated in a retrospective series of 15 patients obtaining a 53% ORR with a median PFS of 7.7 months [68]. This combination deserves to be assessed in prospective trials.

Strategies to consolidate a second remission, such as HDC/ASCT, immunotherapy or BBB disruption, could be considered to improve local control and survival.

4. Expert opinion

In the last decade, Phase II trials demonstrated that PCNSL are a potentially curable disease. Regimens combining HD-MTX and other drugs active in the CNS and followed by WBRT obtain a significant number of durable remissions and ultimately result in a 5-year OS ranging from 30 to 50%, especially for young patients. One of the most relevant methodological constraints in the development of a consensus in the treatment of this disease has been the difficulty to conduct randomized trials. This can be overcome if questions widely perceived as key issues for PCNSL cure or patient quality of life are identified. This was recently demonstrated by an international, randomized Phase II trial, the IELSG #20 trial, which has established that the addition of HD-AraC to HD-MTX is associated with a remarkable outcome benefit in patients with PCNSL and should be considered the control group for future randomized trials.

Despite the benefit of the addition of HD-AraC, present results in patients with PCNSL remain unsatisfactory and the enrolment of PCNSL patients in clinical trials should be always encouraged. According to the therapeutic strategies for aggressive lymphomas used worldwide, PCNSL should not be treated exclusively with antimetabolites, and the assessment of other drugs active against other phases of the tumour cell cycle should be considered for future trials. Some alkylating agents (e.g., temozolomide, ifosfamide, thiotepa and nitrosoureas) are interesting candidates because they can cross the BBB, show antilymphoma activity, are active against phase-G0 cells and increase the cytotoxicity of antimetabolites. Rituximab could be another candidate, especially in view of its safety profile. Its combination with chemotherapy based on HD-MTX was proved to be feasible [15], but rituximab remains to be tested in a randomized setting as there are several doubts about its capability to cross the BBB [58,69]. These studies might consider as a possible strategy optimization of the potential benefit of rituximab to add this drug during the first chemotherapy courses when the BBB is evidently altered by the presence of infiltrating lymphoma.

Although HDC/ASCT seems feasible only in young and fit patients, which excludes a third of those with PCNSL, and could represent a relevant selection bias, this strategy has also produced encouraging results in these lymphomas and could be an alternative to WBRT for consolidation. The replacement of WBRT with HDC/ASCT as consolidation treatment after primary HD-MTX-based chemotherapy could result not only in an improved OS and an ameliorated PFS but also in a significant reduction of iatrogenic neurotoxicity. Furthermore, this strategy would lead to the preservation of a valid option, like WBRT, as salvage therapy in the case of disease relapse. Thus, a comparison between HDC/ASCT and WBRT as consolidation therapy is also a relevant issue to be tested in a randomized setting.

Another frequent problem for physicians dealing with PCNSL is represented by elderly patients for whom few data

Table 3. Salvage therapies for PCNSL.

Treatment	Study	N°	mAge	Prior RT	PS 0 – 1	CR + PR	mPFS	mOS	1-yr OS	N	PLT	Other tox
Topotecan [73]	prospective	27	51	52%	60%	19 + 14%	2.0	8.4	39%	26%	15%	11%
Temozolomide [37,74]	prospective	36	60	86%	28%	25 + 6%	2.8	4.0	31%	6%	3%	3%
Methotrexate [75]	retrospective	22	58	14%	-	73 + 19%	26	26	70%	5%	5%	36%
Temozolomide + Rituximab [68]	retrospective	15	69	13%	67%	40 + 13%	2.2	10.5	58%	7%	27%	7%
VP16 + Ifosfamide + AraC [67]	retrospective	16	54	100%	37%	37 + 0%	4.5	6.0	41%	69%	50%	37%
i.a. Carboplatin ± VP16 ± CTX ± RT [76]	retrospective	37	57	24%	76%	24 + 11%	3.0	6.8	25%	22%	19%	> 30%
Radiotherapy [66]	retrospective	27	67	-	-	37 + 37%	9.7	10.9	49%	-	-	15% neuro
Radiotherapy [65]	retrospective	48	-	-	-	58 + 21%	10.0	16.0	54%	-	-	58% neuro
AraC + VP16→TTP + Busulfan + CTX [39]	prospective	43	52	33%	-	50 + 0%	-	18	-	-	-	TRM: 14%
Intrathecal Rituximab [59]	Phase I	10	56	80%	-	0 + 60%	-	5.2	30%			

mAge: Median age; RT: Radiotherapy; PS: Performance status; CR: Complete response; PR: Partial response; mPFS: Median progression-free survival; mOS: Median overall survival; 1-yr OS: One-year overall survival; N: Grade 3 – 4 neutropenia; PLT: Grade 3 – 4 thrombocytopenia; tox: Toxicity; i.a.: intra-arterial; VP16: Etoposide; HD-AraC: High-dose cytarabine; TTP: Thiotepa; CTX: Cyclophosphamide.

are available and in whom the possibility of using HD-MTX-based approaches might be underestimated [70]. In analogy with other diseases, we believe that fit patients > 65 years might well be able tolerate approaches analogous to those of younger patients with a similar outcome and thus studies including this population, in our opinion, should be encouraged.

In conclusion, there are currently several opportunities to improve the curability rate of PCNSL with integrating and sequential approaches. The best strategy to validate these novel strategies is represented by international cooperation to conduct well-designed multicenter and possibly randomized trials [71]. This goal can be achieved only if a wide general consensus on the crucial questions and possible solutions in the management of PCNSL is accomplished.

In the next 5 years, we will probably find answers regarding: i) the best drug combination for induction; ii) the role of different regimens, including HD-MTX, HD-AraC and rituximab; iii) the best consolidation regimen; and iv) the role of HDC/ASCT versus WBRT. Nevertheless, we believe that to achieve further and substantial improvements in the therapy of PCNSL, a better knowledge of the biological features of PCNSL and their micro-environment is warranted. In this context, data suggesting that two groups of genes involved in the immune response, including regulation of HLA expression, and in apoptosis (e.g., the p53 pathway) might become relevant and deserve further investigation [72]. Similarly, analysis of non-genomic aberrations involving molecules that could be targeted by specific agents (e.g., CD20) could provide information relevant for developing treatment programs. Finally, data from PCNSL genome-wide analysis and whole genome sequencing might generate new and possibly unexpected perspectives for future patients.

Declaration of interest

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