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Primary central nervous system lymphoma: a narrative review of ongoing clinical trials and goals for future studies

Lauren R. Schaff[1], **Prakash Ambady**[2], **Nancy D. Doolittle**[2], **Christian Grommes**[1]

[1]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;

[2]Department of Neurology, Oregon Health & Science University, Portland, OR, USA

Abstract

Primary central nervous system lymphoma (PCNSL) is a rare disease of the brain, spine, cerebrospinal fluid (CSF) and/or vitreoretinal space. PCNSL is chemo and radiosensitive but relapse is common even years after initial treatment. Outside of consensus regarding the use of high-dose methotrexate (HD-MTX) for first line treatment, there is little uniformity in the management of newly diagnosed or relapsed PCNSL. The lack of consensus is driven by a paucity of randomized trials in this disease. Prospective studies are troubled by low enrollment, the lack of a standard induction regimen, and a varied approach to consolidation strategies. Moreover, the PCNSL patient population is heterogeneous and includes a high proportion of elderly or frail patients and consists of patients manifesting disease in varied compartments of the central nervous system (CNS). As a result, current treatment strategies vary widely and are often dictated by physician and institutional preference or regional practice. This review provides an overview of recently completed and ongoing therapeutic studies for patients with newly diagnosed and recurrent or refractory PCNSL. It discusses the existing evidence behind common approaches to induction and consolidation or maintenance regimens as well as the recent data regarding management of recurrent disease. Finally, it highlights the complexity of trial design in this

Correspondence to: Lauren R. Schaff; Christian Grommes. 1275 York Avenue, New York, NY 10065, USA. SchaffL@mskcc.org; GrommesC@mskcc.org.

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disease and provides a framework for the design of future studies, which are needed to identify patient populations likely to benefit from specific induction, consolidation, or maintenance therapies.

Keywords

Primary central nervous system lymphoma (PCNSL); high-dose methotrexate (HD-MTX); autologous stem cell transplant

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare disease affecting the brain, spine, cerebrospinal fluid (CSF), and or/eyes with an incidence of 0.4 per 100,000 person-years (1). While PCNSL is chemo and radiosensitive, relapse is as common as 50% in the first two years (2), highlighting the need for improved durable therapies.

There is little consensus on the management of PCNSL, aside from a general agreement on the importance of high-dose methotrexate (HD-MTX) in the first-line setting. Recommended doses, drug combinations, and duration of therapy are inconsistent, with practitioners often relying on regional and institutional preferences. Variations in treatment can be attributed to the paucity of prospective, randomized clinical trial data. Due to the rarity of PCNSL, phase III studies powered for comparison are difficult to conduct and take many years to produce meaningful results. As a result, many therapeutic trials are single-arm or randomized phase II studies, to be interpreted with caution. Moreover, data generated by successfully completed trials may be of limited generalizability in the clinic. While PCNSL disproportionately affects the elderly with a median age of diagnosis of 67 (3), many trials restrict enrollment to younger patients. As a result, there is a lack of safe and effective treatment options for the elderly population. Additionally, patients may have involvement of multiple central nervous system (CNS) compartments including the CSF or intraocular space. Whether these compartments require dedicated treatment remains unclear as such patients are often underrepresented or under-described in most trials.

This review discusses recently completed and ongoing studies in PCNSL while highlighting the complexity of clinical trial design in this disease. It provides an overview of outstanding questions in the field and the ongoing trials that are attempting to answer them. It also attempts to provide a framework for the design of future studies. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aol-20-47).

Induction therapy

The difficulties of designing a study for PCSNL are highlighted by the paucity of prospective data. The first attempted randomized study in this disease accrued only 53 patients over 7 years and was ultimately terminated due to poor enrollment (4) (Table 1). It was not until 2009 that the first randomized study in PCNSL was published. The phase II trial compared HD-MTX monotherapy (3.5 g/m^2) to HD-MTX (3.5 g/m^2) + high-dose

cytarabine. While the study was not powered for comparison between arms, data favored combination therapy with a complete remission rate (CRR) of 18% *vs.* 46% (primary endpoint), a 3-year failure-free survival of 21% *vs.* 38% and a 3-year overall survival (OS) of 32% *vs.* 46% (12). Rather than defining a new standard for induction, this study was interpreted to indicate polychemotherapy with HD-MTX-based treatment is superior to HD-MTX alone. Several single arm phase II studies seemingly found success with alternate induction polychemotherapy regimens that combine MTX with an alkylating agent. Popular regimens include HD-MTX, carmustine, etoposide, and prednisone (MBVP); HD-MTX, vincristine, and procarbazine (MVP); and HD-MTX, temozolomide, and rituximab (R-MT) to highlight a few (19,25,30–32). With increasing concern over the inadequacy of HD-MTX monotherapy, the German Primary CNS Lymphoma Study Group (G-PCNSL-SG) amended their ongoing trial in 2006 to include the addition of ifosfamide to MTX 4 g/m^2 in the induction regimen (9). Notably, many of the studied combination regimens use MTX dosed 3–4 g/m^2. An unanswered question is whether higher doses of MTX may be more effective and obviate the need for combination treatment. In 2003 the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium published a study of 8 g/m^2 MTX monotherapy that demonstrated response rates comparable to historical controls [CRR 52%, overall response rate (ORR) 74%) with only modest toxicity (48% grade 3 or 4 events] (16).

To date, only a handful of randomized studies comparing induction strategies have been published. In 2016, the International Extranodal Lymphoma Study Group-32 (IELSG32) compared HD-MTX + high-dose cytarabine; HD-MTX, high-dose cytarabine + rituximab; and HD-MTX, high-dose cytarabine, rituximab, + thiotepa (MATRix). The study was not powered for comparison between arms limiting interpretation though CRR of 49% (primary endpoint) appeared superior in the MATRix arm of treatment. The addition of rituximab to HD-MTX and cytarabine appeared to result in improved CRR to 30% from 23% with HD-MTX and cytarabine alone (2). An important criticism of this study is the seemingly poor outcomes of the control arm. While the IELSG32 saw a CRR of 23% and ORR of 53% with HD-MTX + high-dose cytarabine, the same regimen resulted in a CRR 46% with ORR 69% seven years prior (2,12). The authors argue the data reflects different patient populations with the IELSG32 study enrolling more patients with high-risk features such as increased elevated serum LDH and CSF protein, presence of meningeal spread and involvement of deep structures (2). Currently the MATRix protocol is being used as the induction regimen for an ongoing phase III clinical trial comparing consolidation therapies (NCT02531841) (Table 2). It remains to be seen whether its use will be widely adopted as standard practice across the globe.

Challenging the results of the IELSG32 and earlier retrospective data (33), the Cooperative Trial of the Hemato-Oncologie voor Volwassenen Nederland (HOVON) and Australasian Leukaemia and Lymphoma Group (ALLG) recently published a phase III randomized trial (HOVON 105/ALLG NHL 24) addressing the role of rituximab in first-line treatment for PCNSL. The study enrolled 200 patients over 6 years to receive HD-MTX, carmustine, teniposide, and prednisone, with or without rituximab. Patients with response received consolidation with high-dose cytarabine and, if 60 years of age or younger, whole-brain radiotherapy (WBRT). Ultimately, the study found no statistical difference in their primary endpoint of event free survival (EFS) at one year (49% without rituximab *vs.* 52% with

rituximab) (23). While the authors did comment on a trend toward improved EFS with rituximab in younger patients, the significance of this is unclear as the study was not sufficiently powered to address this question. The results of this phase III study highlight some of the difficulties in trial design for a heterogeneous population and the dangers of over-interpreting non-comparative phase II data. With conflicting results and the relative tolerability of rituximab, many practitioners have continued to incorporate rituximab into treatment regimens and it is still being used in many ongoing clinical trials. For example, LOC-R01 will include rituximab with MVP plus lenalidomide or ibrutinib for the treatment of newly diagnosed patients aged 18–60 (NCT04446962).

Rare studies have taken the novel approach of omitting HD-MTX from first-line treatment entirely. After a 2014 study of fotemustine, teniposide, and dexamethasone (FTD) appeared to demonstrate comparable efficacy to historical controls (34), a phase II study compared this regimen to HD-MTX + high-dose cytarabine. The regimens appeared to yield similar results with ORR 88% in the FTD arm *vs.* 84% with HD-MTX + high-dose cytarabine though the sample size of 49 patients was small, limiting interpretation (14). Interestingly, a higher incidence of cognitive decline following WBRT was reported in the HD-MTX arm. As such, the FTD regimen warrants further study for patients with contra-indication to HD-MTX or planned for radiation.

Other studies are attempting to optimize MTX delivery. Doses required to achieve cytotoxic drug concentrations in the CSF can result in acute renal or hepatic injury, pneumonitis, and bone marrow suppression (35). Dose reduction or premature cessation of therapy is not uncommon, particularly in the elderly population (36,37). Intra-arterial (IA)-MTX with blood brain barrier disruption (BBBD) may allow for increased chemotherapy penetration into the CNS, potentially improving efficacy or reducing dose of MTX required to achieve desired results. A multi-center study of IA MTX with BBBD demonstrated ORR 81.9% (CRR 57.8%) with OS 3.1 years, comparing favorably to historical controls. Notably, approximately half the patients in the study were aged 60 or older and did not undergo consolidation therapy (38). Prospective neuropsychological tests demonstrated preservation of cognitive functioning from the end of treatment to a median follow up 12 years after diagnosis (39). Use of IA MTX and BBBD remains under investigation with an ongoing study enrolling patients with newly diagnosed PCNSL for treatment with IA MTX, rituximab and carboplatin with BBBD (NCT00293475).

Empiric use of glucarpidase is another potential strategy for enhancing MTX delivery. Glucarpidase is a bacterial recombinant enzyme that results in rapid clearance of systemic MTX. It is currently approved by the Food and Drug Administration for use in patients with MTX toxicity and acute renal failure. CSF MTX concentrations do not appear affected by glucarpidase as it does not cross the blood brain barrier (40). Its use is currently being investigated in PCNSL to achieve rapid systemic MTX clearance without impact on efficacy in the CNS. Preliminary data from our ongoing study demonstrates glucarpidase can be given throughout MTX treatment. CSF MTX concentrations appear to remain cytotoxic following glucarpidase administration and clinical response to MTX is appreciated (41). Further investigation is needed to determine whether use of glucarpidase might prevent need for MTX dose reduction, which can be required in as many as 75% of patients (37).

Currently we are utilizing glucarpidase to investigate feasibility of outpatient HD-MTX administration (NCT03684980).

Consolidation therapy

The optimal consolidation regimen for PCNSL has yet to be elucidated and likely differs based on patient and disease characteristics. While WBRT was the mainstay of treatment for many years, cognitive deficits and lackluster survival data have led to the exploration of other options. In 2010, the first phase III study conducted in PCNSL attempted to address the need for WBRT. Designed as a non-inferiority trial, the study randomized patients with a complete response (CR) following MTX-based treatment to receive WBRT 36 Gy or undergo observation. Patients without a CR were randomized to WBRT (36–40 Gy with 9 Gy boost) or high-dose cytarabine. While the study detected no significant difference in OS between treatment groups (32.4 months with WBRT *vs.* 37.1 without WBRT), it failed to meet the pre-determined non-inferiority margin (9). The study collected little cognitive data but did report clinical neurotoxicity in 49% of assessable patients treated with WBRT as compared to 26% of patients who did not receive WBRT. These findings, particularly in patients aged 60 and older, are consistent with those previously reported (42,43).

Whether low dose WBRT may reduce neurotoxicity without compromising disease control remains to be seen. A single arm study of WBRT 23.4 Gy following rituximab-MVP-cytarabine (R-MVP-A) yielded an ORR of 78% and median progression-free survival (PFS) of 7.7 months (10). There was no impact on cognition initially reported however, a decline in attention and executive functioning was detected after 3 years, following an initial improvement (44). RTOG 1114 is an ongoing randomized trial comparing R-MVP-A with WBRT 23.4 Gy to R-MVP-A alone. Preliminary results presented at the American Society of Clinical Oncology (ASCO) 2020 meeting demonstrate improved 2-year PFS in the radiation arm (78% *vs.* 54%) with median OS not reached in either arm (45). In these preliminary results, neurotoxicity did not appear to differ between the two arms though long term follow up is required.

Based on the ongoing concerns surrounding WBRT, many in the field have sought alternate methods of consolidation. Myeloablative high-dose chemotherapy followed by autosomal stem cell transplant (HDC-ASCT) offers the benefit of increased drug concentrations in the CNS and may allow for disease control without the need for radiation. Recent data on HDC-ASCT suggest this is a promising strategy for patients who are eligible. Two single-arm phase II studies of HDC-ASCT following MTX-based induction yielded ORR >90% with prolonged PFS and median OS not yet reached (27,28). Notably, both these studies utilized thiotepa-based consolidation regimens and yielded superior results to historical studies in which BCNU-based regimens were utilized (24,25,46).

Early results of two randomized studies exploring the efficacy and tolerability of HDC-ASCT were recently published. IELSG32 randomized all patients with stable disease or response after induction therapy (HD-MTX + Ara-C ± rituximab ± thiotepa) to receive 36 Gy WBRT or HDC-ASCT with carmustine and thiotepa conditioning. Initial results suggest no significant difference in the primary end point (2-year PFS 80% WBRT *vs.* 69% HDC-

ASCT) (47). Of note, only 50–60% of patients in each induction arm proceeded to the second phase of randomization, again highlighting the poor outcomes seen in the induction portion of this study (2). The phase II PRECIS study similarly randomized patients to receive WBRT (40 Gy) or HDC-ASCT. Both arms met the pre-determined threshold for efficacy with 2-year PFS 63% in the WBRT arm and 87% in the HDC-ASCT arm (29). Neither study was powered for comparison, limiting interpretation. Cognitive decline was noted after WBRT in both studies while patients treated with HDC-ASCT had improved cognition at two or three years of follow up (29,47). Continued long term assessment will be required as decline in executive functioning more than three years following HDC-ASCT has been reported (44).

Early studies of HDC-ASCT largely limited eligibility to patients younger than 60–70 (26,27,29,47,48). Only recently was this method of consolidation prospectively explored in a population that included patients >70 years of age. Schorb *et al.* reported that HDC-ASCT with busulfan/thiotepa conditioning was feasible and well tolerated in a carefully selected group of fourteen patients with a median age of 74 (range, 69–79) with no treatment related deaths (49). However only 40% of screened patients met eligibility for enrollment, highlighting the fact that there is a subset of patients, predominantly the elderly, for whom HDC-ASCT is not an option and whom are high risk for neurotoxicity with WBRT. In these patients, consolidation strategies consist of non-myeloablative chemotherapy or maintenance therapy. It is an open question whether either strategy is as efficacious as radiation or HDC-ASCT. Encouragingly, a single arm phase II study of R-MT followed by consolidation with etoposide and cytarabine yielded responses comparable with historical controls (ORR 72%, PFS 48 months) (19). CALGB (Alliance) 51101 randomized patients to consolidation with non-myeloblastic chemotherapy with cytarabine and etoposide *vs.* HDC-ASCT with thiotepa and carmustine conditioning. Preliminary results reporting response to the induction regimen were disappointing with only two-thirds of patients proceeding to consolidation (37) however, results of the consolidation phase are pending (NCT01511562). IELSG43 is another ongoing study which randomizes patients after response to MATRix induction therapy to receive either HDC-ASCT with carmustine/thiotepa conditioning or a nonmyeloablative regimen of rituximab, dexamethasone, etoposide, ifosfamide, and carboplatin (NCT02531841).

Ongoing maintenance therapy, rather than consolidation, is another potential treatment strategy. Two early phase prospective trials support the use of TMZ maintenance. RTOG 0227 treated patients with R-MT followed by WBRT and temozolomide 200 mg/m^2 days 1–5 every 4 weeks. The study reported an ORR of 87.5% and a 2-year OS of 81% (32). Notably the Nordic Lymphoma Group also utilized TMZ maintenance though in an elderly population and following age-adjusted MTX and cytarabine. This study omitted WBRT and saw 2-year OS of 60% (50). Unfortunately a phase III study comparing WBRT to WBRT with concurrent and then maintenance TMZ following HD-MTX was recently terminated due to futility after 134 patients were enrolled (51) raising the question of benefit of maintenance TMZ. Complicating interpretation of this study is the potentially sub-optimal induction chemotherapy regimen of HD-MTX monotherapy. Further light may be shed on this issue with the completion of BLOCAGE-01, a phase III study of patients with CR

following HD-MTX, randomized to receive seven cycles of R-MT or no further treatment (NCT02313389).

Multiple studies have also provided evidence for maintenance with rituximab, procarbazine, ibrutinib, and lenalidomide (22,52–55). Based on reports which suggest maintenance rituximab may prolong disease control (52,55) a multi-center randomized phase II study was developed to evaluate the effect of maintenance obinutuzumab on CR duration in patients who attain a CR to first-line HD-MTX-based chemotherapy (NCT02498951). Ongoing studies with obinutuzumab and nivolumab maintenance will further add to our understanding of the role of immunotherapy in this disease and may provide a treatment alternative to prolong response duration for elderly and high risk patients, with minimal toxicity (NCT04401774, NCT04022980). An additional study in the elderly population is examining the role of ibrutinib maintenance following response to HD-MTX based therapy (NCT02623010). FIORELLA, a phase II study of patients ≥70, will eventually provide robust data as patients who are considered eligible for HD-MTX will receive induction HD-MTX, procarbazine, and rituximab then be randomized to receive either procarbazine or lenalidomide maintenance. Alternatively, patients unable to tolerate HD-MTX will receive WBRT with concurrent TMZ and rituximab followed by maintenance TMZ (NCT03495960).

Recurrent/refractory disease

Despite aggressive treatment, 15% of PCNSL cases are refractory to first-line therapy and the probability of recurrence after initial response remains high (56). There is no consensus on disease management in these settings as there are few prospective studies and no randomized trials. A variety of chemotherapeutic options have been studied and have demonstrated modest responses including MTX rechallenge, temozolomide, pemetrexed, topotecan, and rituximab (57–62) (Table 3).

Increased understanding of the pathophysiology of PCNSL has led to developments in targeted therapy. PCNSL harbors frequent mutations in the B-cell receptor (BCR) and toll-like receptor (TLR) pathways, mediated in part by Bruton tyrosine kinase (BTK). Ibrutinib is a BTK inhibitor that has been shown to induce response in recurrent/refractory PCNSL and is detectable in the CSF at concentrations necessary to induce BTK inhibition (71). Ibrutinib has demonstrated efficacy both as a single agent (69,72), and in combination with alkylating therapy (72) as well as MTX/rituximab (53). It has also been studied as a maintenance agent (53) though data suggests early resistance mechanisms are a concern. Currently, multiple studies are ongoing combining ibrutinib with alternate treatment strategies including rituximab and lenalidomide (NCT03703167), copanlisib (NCT03581942), check point inhibition (NCT04421560, NCT03770416), and traditional chemotherapies such as ifosfamide and etoposide (NCT04066920). Acalabrutinib is a second generation BTK inhibitor approved for treatment of chronic and small lymphocytic leukemias as well as mantle cell lymphoma and will be tested in an upcoming phase I study for newly diagnosed PCNSL patients unable to tolerate HD-MTX (NCT04462328).

Alterations of the PI3K/mTOR pathway are also commonly detected in PCNSL. Early attempts to inhibit mTOR with temsirolimus yielded disappointing results. Initial radiographic findings suggested early response however, PFS was only 2.1 months suggesting development of resistance (65). Notably, CSF concentrations of temsirolimus were detected in only one of nine tested patients, suggesting poor CNS penetration (65). Current studies are ongoing for two additional agents targeting this pathway: PQR309, a dual PI3K/mTOR inhibitor (NCT02669511), and copanlisib, a PI3K inhibitor (NCT03581942). Both drugs are being studied in recurrent/refractory PCNSL. To address concerns regarding resistance, copanlisib is being combined with ibrutinib (73). The study is also open to newly diagnosed patients with contra-indications to HD-MTX.

Immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide are also being investigated for use in PCNSL. A phase I study of lenalidomide alone and in combination with intrathecal rituximab demonstrated an objective response in nine of 14 patients. Notably, lenalidomide was detected in the CSF in dose-dependent concentrations (74). In a multi-center phase II study, lenalidomide was administered with rituximab followed by lenalidomide maintenance for responders. The primary objective was ORR at the end of induction therapy. Best observed responses during induction resulted in an ORR 63% (16/43 CR, 11/43 PR) however by the end of induction, ORR was 39%. Results of the maintenance phase are pending (54). Current studies combining lenalidomide with ibrutinib (NCT03703167) and MTX-based regimens, (NCT04129710, NCT04446962) are underway in recurrent/refractory disease. It is also being studied as maintenance therapy for newly diagnosed disease (NCT04120350, NCT03495960). Pomalidomide, a third general IMiD has also demonstrated some efficacy in PCNSL through a phase I dose escalation study (67). It is currently being studied in conjunction with nivolumab for patients with recurrent/refractory PCNSL or primary vitreoretinal disease (NCT03798314).

Immunotherapy is of increasing interest in the treatment of PCNSL. PD-1 ligand deregulation is seen in >50% of PCNSL suggesting a role for PD-1 inhibition (75). A small retrospective study that included 4 patients with PCNSL demonstrated PFS between 14–17 months and in two patients, a durable response >12 months (76). A more recent study of PD-1 blockade in combination with rituximab in 6 patients with recurrent PCNSL or isolated CNS relapse of systemic lymphoma yielded a 50% CRR. One patient in the series experienced progression after cessation of therapy and re-attained CR with re-initiation of PD-1 blockade (77). Currently PD-1 blockade is being studied in the monotherapy setting (NCT02857426, NCT02779101), in conjunction with other agents such as ibrutinib (NCT03770416, NCT04421560) or pomalidomide (NCT03798314) and as a maintenance/consolidation strategy (NCT04401774, NCT04022980). PDL-1 blockade is also being studied in a single institution phase 1 study (NCT04462328). Chimeric antigen receptor-T (CAR-T) cells are an exciting and novel strategy in systemic lymphoma. Initial concerns regarding neurotoxicity and impaired T-cell expansion in the absence of systemic disease led to the exclusion of PCNSL patients from early CAR-T trials. NCT02631044 allowed enrollment of patients with secondary CNS involvement in the presence of systemic disease and reported on a singular case of a patient achieving a CR in the brain following therapy with JCAR017, a CD19-directed CAR-T cell product (78). Since this time, a retrospective report of patients treated with off-label tisagenlecleucel, another CD19-directed CAR-T,

yielded responses in 4/8 patients with minimal toxicity and evidence of T-cell expansion even in patients with isolated CNS disease (79). A study investigating the use of tisagenlecleucel in PCNSL is currently recruiting (NCT04134117).

Goals for future studies

Despite the recently completed and ongoing studies in PCNSL, a number of outstanding questions remain unanswered. To advance this field, more well-designed appropriately-powered clinical trials are needed. An important limitation however, is the rarity of PCNSL in the general population. This issue can be addressed in two ways: by increasing the number of patients enrolled onto study and by maximizing efficiency of the studies performed. Whenever possible, PCNSL patients should be referred to a specialized cancer center where they may be enrolled on an investigational protocol. Investigators designing trials should be mindful of overly restrictive eligibility criteria that may unnecessarily exclude patients (80). Randomized control trials offer the most reliable data and serve as the gold standard in evidence-based medicine however, a large number of patients is necessary for their completion. The field of neuro-oncology has begun to circumvent this problem in the treatment of glioma by opening multi-center, multi-arm platform studies with comparison of several experimental therapies to a single contemporary control arm (81). Such platforms are optimal for rare diseases as they allow for a reduction in the overall number of contemporary control patients necessary to answer multiple scientific questions simultaneously. Such a strategy may be considered in the future of PCNSL but would require some consensus in the field regarding an appropriate control. In the meantime, multi-stage studies such as IELSG32 with more than one randomization, maximize efficiency by attempting to answer two different questions with the same study group (2).

An important factor to consider in trial design is the achievability of the primary endpoint. While demonstration of improved OS is optimal, such studies can take years to mature before yielding meaningful data. As a result, many studies are appropriately opting for shorter endpoints such as CRR, ORR, or pre-determined points of assessment of PFS or OS. This problem may be aided by the identification of novel bio or imaging markers that could be used to assess response. For example, detection of ct-DNA in the CSF of PCNSL patients appears associated with treatment response and/or relapse (53). This biomarker is now being used to determine eligibility for maintenance therapy in an ongoing phase II study (NCT04401774). Further data is needed to determine whether its presence might serve as a surrogate endpoint. Concentration of interleukin-10 in the CSF has also been associated with treatment response and duration (68,82). Imaging biomarkers are also the source of much interest with recent work suggesting correlations between perfusion imaging, diffusion-weighted sequences, or texture parameters to outcome measures (83–86).

To further optimize clinical studies, it is essential we are studying the correct treatments. Only therapeutics with sound biologic rationale and promising early phase clinical data should be brought to a larger setting. Efficacy stopping rules should be in place in the event of an unsuccessful therapy. In the study of novel agents, it is crucial to incorporate tissue sampling (CSF or biopsy if able) to gather pharmacokinetic data. CSF is often used as a surrogate for brain parenchyma but pharmacokinetics are likely different between these

spaces. Notably, temsirolimus was detected at adequate concentrations in glioma tissue (87) however was not detectable in the CSF in eight of nine patients with PCNSL (65).

Trials involving new therapies or enrolling the elderly should include robust assessment of neurocognitive functioning and quality of life metrics as the minimization of neurotoxicity is a primary goal in PCNSL treatment. As PCNSL treatments intensify, durable remission rates and survival are expected to increase. Increased survival in combination with intact cognitive abilities is an important benchmark for determining optimum PCNSL therapies. While early studies relied on the Mini Mental Status Exam (MMSE), this is an insensitive test for cognitive decline in PCNSL (88). A standard battery of cognitive tests would allow for comparison across trials. The specific battery proposed by Correa *et al.* in conjunction with the International PCNSL Collaborative Group (IPCG) has the benefit of testing across multiple cognitive domains, is easy to administer, has been translated into several languages, and has demonstrated high retest reliability (88). Imaging biomarkers including quantification of T2 signal change on magnetic resonance imaging (MRI) and analysis of diffusion tensor imaging (DTI) should be assessed whenever feasible as they have been associated with cognitive decline after cancer-directed treatment (43,89). Analysis of functional MRI may be beneficial in predicting patients at risk for treatment-related cognitive impairment and following change in brain function (90,91). All studies should include prospective pre-treatment and long term follow up whenever possible.

Summary

While there is no consensus on the exact management of PCNSL, general guidelines are agreed upon. These include the use of HD-MTX for induction therapy when possible, followed by consolidation or maintenance. Recommendations for consolidation/maintenance should ideally be tailored to individual patients, taking into account age, performance status, general medical health, and response to induction treatment.

The use of novel targeted agents and immunotherapies are currently being investigated in PCNSL and hold much promise. Optimization of clinical trial design and enrollment is needed to streamline study of these new approaches and hopefully render a new standard of care.

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Table 1

Historic first-line clinical trials

Author	Agent(s)	Trial start†	Phase	Randomized (Y/N)	Evaluable subjects	CR rates (%)	OS (months)	Participant age
Radiation alone								
Nelson (5)	WBRT [60]	1983	2	N	41	NA	11.6	18+
Chemoradiation								
DeAngelis (6)	M [2.5]+V [1.4]+P [100]+IT-M+WBRT [45]+AraC [3]	1993	2	N	98	58	36.9	Not specified
Ghesquieres (7)	C5R; WBRT patients younger than 60 years (group 1, n=45) received full C5R (COP, COPADEM, CYM). Patients aged 61–70 years (group 2, n=36) received reduced doses (COP, MCOPA, CYM). Patients older than 70 years (group 3, n=18) received four courses of MCVP	1995	2	N	99	49	33	18+
Poortmans (8)	M [3]+ten [100]+B [100]+pred+IT-M+IT-A +WBRT [40]	1977	2	N	52	69	46	16–75
Thiel (9)	M [3]±WBRT [45]	2000	3	Y	411	41 (M+WBRT) *vs.* 41 (M)	32 (M+WBRT) *vs.* 37 (M)	18+
Morris (10)	R [500]+M [3.5]+P [100]+V [1.4]; WBRT [23.4]+AraC [3]	2002	2	N	43	79	NA	18+
Laack (11)	WBRT [41.4+9]+pred	2003	2	N	19	16	6	70+
Ferreri (12)	M [3.5]±AraC [2]; WBRT	2005	2	Y	79	18 (M) *vs.* 46 (M +AraC)	Not reached	18–75
Wang (13)	WBR [40]+TMZ [75]; TNV	2007	2	N	14	86	NA	Not specified
Wu (14)	FTD vs. M [3.5]+AraC [1]; WBRT [30]	2012	2	Y	49	33 (FTD) *vs.* 40 (M+AraC)	6.6 years	14–69
Adhikari (15)	R [375]+M [3.5]+V [1.4]+P [100]; WBRT [23.4 or 45]; AraC [3]	2015	2	N	19	53	19	NA
Chemotherapy alone								
Batchelor and Gerstner (16,17)	M [8]	1996	2	N	25		55.4	≥18
Herrlinger (18)	M [8]	1998	3	N	37	30	25	Not specified
Rubenstein (19)	M [8]+T [150]+R [375]; Eto [40]+AraC [2]	2004	2	N	44	66	Not reached	Any age
Chamberlain (20)	M [8]+R [375]	2000	2	N	40	60	29.0	18–93

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Author	Agent(s)	Trial start†	Phase	Randomized (Y/N)	Evaluable subjects	CR rates (%)	OS (months)	Participant age
Omuro (21)	M [3.5]+TMZ [150] *vs.* M [3.5]+P [100]+V [1.4]+AraC [3]	2007	2	Y	95	NA	14 (M+TMZ) *vs.* 31 (MPV)	60 years and older
Fritsch (22)	R [375]+M [3]+P [6]	2009	2	N	28	64	18	≥65
Bromberg (23)	M [3]+B [100]+ten [100]+pred±R [375]; AraC [2]. Patients <60 received WBRT	2010	3	Y	200	66 (MBVP)‡ *vs.* 68 (R-MBV)‡	56.7 (MBVP) *vs.* not reached (R-MBVP)	18–70
Ferreri (2)	M [3.5]+AraC [2]±R [375]±thio [30]	2010	2	Y	219	49	Not reached	18–70
ASCT								
Abrey (24)	M [3.5]+AraC [3]; BEAM	NA	2	N	28 (14 ASCT)	NA	Not reached	Not specified
Colombat (25)	M [3]+B [100]+Eto [100]+pred; BEAM+RT [30]	1999	2	N	25 (17 ASCT)	44	40	≤60 years
Illerhaus (26)	M [8]+AraC [3]+thio [40]; B [400]+thio (5 mg/kg)+RT [45]	1998	2	N	30 (23 ASCT)	33	Not reached	18–65
Illerhaus (27)	R [375]+M [8]+AraC [3]+thio [40]; R [375]+B [400]+thio (5 mg/kg)	NA	2	N	79 (75 ASCT)	77.2	NA	18–65
Omuro (28)	R [500]+M [3.5]+P [100]+V [1.4]; thio [250]+cyclo [60]+bus [3.2]	2005	2	Y	32 (26 ASCT)	81	NA	18 to 72
Houillier (29)	R [375]+M [3]+B [100]+Eto [100]+pred followed by randomization to WBRT [40] *vs.* ASCT	2008	140	2	Y	64 (WBRT) *vs.* 49 (ASCT)	NA	18–60

†, registration date on clinicaltrials.gov;

‡, CR after cytarabine and WBRT consolidation. ASCT, autosomal stem cell transplant; AraC, cytarabine (g/m^2); B, carmustine (mg/m^2); BEAM, carmustine, etoposide, cytarabine, melphalan; bus, busulfan (mg/kg); COP, cyclophosphamide, vincristine, prednisone; COPADEM, methotrexate (3 g/m^2), cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; cyclo, cyclophosphamide (mg/m^2); CYM, methotrexate (3 g/m^2), cytarabine; Eto, etoposide (mg/m^2); FTD, fotemustine, teniposide, dexamethasone; IT-A, intrathecal cytarabine, IT-M, intrathecal methotrexate; MCOPA, vincristine, methotrexate (1.5 g/m^2), doxorubicin, cyclophosphamide, prednisone MCVP, methotrexate (1.5 g/m^2), cyclophosphamide, etoposide, prednisone; M, methotrexate (g/m^2); OS, overall survival; P, procarbazine (mg/m^2/day); PR, partial response; pred, methylprednisolone; R, rituximab (mg/m^2); ten, teniposide (mg/m^2); thio, thiotepa (mg/m^2); TMZ, temozolomide (mg/m^2); TNV, temozolomide, nedaplatin, vincristine; V, vincristine (mg/m^2); WBRT, whole brain radiotherapy (Gy).

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Table 2

Ongoing clinical trials

Agent(s)	Clinical Trials.gov ID	Trial start date	Phase	Randomized (Y/N)	Eligible age (yrs)	Country (location of coordinating center)
Induction						
Rituximab, MTX, prednisone, vincristine; and lenalidomide or ibrutinib	NCT04446962	2020	1b/2	Y	18 to 60	France
IA MTX, carboplatin and IV rituximab, with BBBD	NCT00293475	2006	2	N	18 to 75	USA
Glucarpidase following MTX and rituximab	NCT03684980	2018	1	N	18+	USA
Consolidation						
HDC-ASCT with thiotepa and carmustine conditioning versus non-myeloablative chemotherapy with cytarabine and etoposide	NCT01511562	2012	2	Y	18 to 75	USA
HDC-ASCT with thiotepa and carmustine versus non-myeloablative rituximab, dexamethasone, etoposide, ifosfamide, and carboplatin	NCT02531841	2014	3	Y	18 to 65; or 66–70 (if ECOG 2 or less)	Germany
Maintenance						
MTX, temozolomide and rituximab, versus observation	NCT02313389	2015	3	Y	60+	France
Obinutuzumab versus observation	NCT02498951	2016	2	Y	18+	USA
Nivolumab	NCT04401774	2020	2	N	18+	USA
Nivolumab	NCT04022980	2019	1b	N	65+	USA
Ibrutinib	NCT02623010	2016	2	N	60 to 85	Israel
Procarbazine or lenalidomide; or temozolomide	NCT03495960	2019	2	Y	70+	Italy
MTX, rituximab, lenalidomide, with lenalidomide maintenance	NCT04120350	2019	1b/2	N	18 to 75	China
Recurrent/refractory						
Ibrutinib with rituximab and lenalidomide	NCT03703167	2019	1b	N	18+	USA
Copanlisib with ibrutinib	NCT03581942	2018	1b/2	N	18+	USA
Pembrolizumab, ibrutinib, and rituximab	NCT04421560	2020	1b/2	N	18+	USA
Nivolumab and ibrutinib	NCT03770416	2019	2	N	18+	USA
Ibrutinib, rituximab, ifosfamide and etoposide, with ibrutinib maintenance	NCT04066920	2019	2	N	20 to 79	Korea
Acalabrutinib and durvalumab	NCT04462328	2020	1	N	18+	USA
PQR309	NCT02669511	2015	2	N	18+	Germany
Ibrutinib versus lenalidomide, with MTX-based regimen	NCT04129710	2020	2	Y	18 to 75	China
Nivolumab and pomalidomide	NCT03798314	2019	1	N	18+	USA

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Agent(s)	Clinical Trials.gov ID	Trial start date	Phase	Randomized (Y/N)	Eligible age (yrs)	Country (location of coordinating center)
Nivolumab	NCT02857426	2016	2	N	18+	USA
Pembrolizumab	NCT02779101	2016	2	N	18+	Austria
Nivolumab and ibrutinib	NCT03770416	2019	2	N	18+	USA
Pembrolizumab, ibrutinib and rituximab	NCT04421560	2020	1b/2	N	18+	USA
JCAR017	NCT02631044	2016	1	N	18+	USA
Tisagenlecleucel	NCT04134117	2019	1	N	18+	USA

ASCT, autologous stem cell transplantation; BBBD, blood-brain barrier disruption; HDC, high-dose chemotherapy; IA, intra-arterial; MTX, methotrexate.

Table 3

Prospective trials in recurrent/refractory PCNSL

Author	Agent(s)	Trial start†	Phase	Randomized (Y/N)	Evaluable subjects	CR rates (%)	OS (months)	Age
Nayak (59)	Rituximab + temozolomide + methylprednisolone	2005	2	N	16	14	Not reported	18+
Reni (63)	Temozolomide	2000	2	N	36	25	3.9	17+
Fischer (61)	Topotecan	2000	2	N	27	19	8.4	18+
Soussain (64)	Cytarabine + etoposide followed by ASCT	2008	2	N	43	35	18.3	18–60
Batchelor (62)	Rituximab	2003	2	N	42	36	20.9	18+
Raizer (60)	Pemetrexed disodium	2006	2	N	11	36	10.1	18+
Korfel (65)	Temsirolimus	2009	2	N	37	13.5	3.7	18+
Rubenstein (66)	IT (R+M)	2005	1	N	14 (6 PCNSL)	43 (CSF and brain), 75% CSF	NR	18+
Grommes (53)	Ibrutinib + M (3.5) + rituximab	2014	1B/2	N	15 (9 PCNSL)	53	NA	18+
Tun (67)	Pomalidomide + dexamethasone	2012	1	N	29	32 for whole study vs. 37.5 in the MTD cohort	NA	18+
Rubenstein (68)	Lenalidomide + rituximab followed by lenalidomide maintenance	2012	1	N	14 (6 PCNSL)	33	NA	18+
Ghesquieres (54)	Lenalidomide + rituximab	2013	2	N	50 (PCNSL34)	29	7.8	18+
Soussain (69)	Ibrutinib	2015	2	N	52	19	19.2	18+
Kasenda (70)	Rituximab + cytarabine + thiotepa followed by HDC-ASCT with rituximab + carmustine + thiotepa	2008	2	N	39	56	18.3	18+
Grommes (71)	Ibrutinib	2014	Ib	N	20 (13 PCNSL)	47	15	18+

†, registration date on clinicaltrials.gov. ASCT, autosomal stem cell transplant; HDC, high-dose chemotherapy; IT, intrathecal; M, methotrexate; R, rituximab.