Relapsed and refractory primary CNS lymphoma: treatment approaches in routine practice

Prakash Ambady¹, Nancy D. Doolittle¹, Christopher P. Fox²,³

¹Department of Neurology, Neuro-Oncology and Blood Brain Barrier Program, Oregon Health & Science University, Portland, Oregon, USA
²Department of Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, UK
³Division of Cancer and Stem Cells, School of Medicine, University of Nottingham, Nottingham, UK

Abstract

Despite recent therapeutic progress and improved survival for many patients with primary central nervous system lymphoma (PCNSL), up to 50% of patients will experience refractory or relapsed disease following first-line treatment with high dose methotrexate (HD-MTX) based regimens. The majority of such events occur within 2 years of diagnosis although, unlike their systemic counterpart, the risk of PCNSL relapse remains, even for patients in radiologic complete response at 10 years following diagnosis. Currently, there are no approved therapies, and no widely accepted ‘standard-of-care’ approaches for the treatment of refractory or recurrent primary central nervous system lymphoma (rrPCNSL). Re-treatment with HD-MTX based regimens, use of non-cross resistant chemotherapy regimens, high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT), and brain irradiation all remain important therapeutic approaches for rrPCNSL. However, the survival outcomes for patients with rrPCNSL remain extremely poor.
and the vast majority of patients will die of their disease. Increasingly, novel treatment approaches are being investigated in early phase clinical studies. Importantly, such therapies need to be evaluated in the context of both refractory and relapsed disease; in older patients and those with co-morbid conditions; and those with neurocognitive dysfunction. A deeper understanding of the molecular genetic mechanisms underpinning rrPCNSL and its unique tumor microenvironment is urgently needed to inform biologically rational and effective therapies. rrPCNSL remains a clear unmet clinical need and a high priority area for clinical research that will require national and international collaborative studies with embedded translational science in order to improve outcomes for patients.

Keywords
Primary central nervous system lymphoma (PCNSL); high-dose therapy; autologous stem cell transplant; high dose methotrexate (HD-MTX); blood brain barrier (BBB); BTKi; immunomodulatory

Introduction
Primary central nervous system lymphoma (PCNSL) is a rare sub-type of diffuse large B-cell lymphoma (DLBCL) that is exclusively confined to the central nervous system (CNS), including brain/spinal tissue and/or leptomeninges and/or vitreo-retinal compartment (1,2). Although these tumor cells appear similar to systemic DLBCL by histopathology, our understanding of the lymphoma biology and neurotrophism seen in PCNSL is still evolving. For the vast majority of patients, high dose methotrexate (HD-MTX) based regimens with rituximab form the backbone of first line remission-induction therapy for newly diagnosed patients with PCNSL. Eligible patients are typically offered consolidation therapy to improve the remission quality and survival outcomes. Although excellent responses are typically achieved and long term survivors are frequently seen (3), by contrast to systemic DLBCL, the risk of relapse after first-line therapy does not plateau even for those patients with sustained complete response (CR) for over 10 years of follow up (4–6). Re-biopsy is often difficult and not routinely performed at disease relapse/progression. Thus, most available data is derived from tissue obtained at initial diagnosis, further limiting our understanding of the patho-biology in rrPCNSL. In the setting of rrPCNSL, the optimal salvage regimen for patients remains elusive. We summarize selected prospective trials in rrPCNSL in Table 1.

PCNSL tends to recur at distinct anatomical locations from the primary tumor within the CNS and/or in the vitreoretinal compartment (16,17), but the mechanisms underpinning treatment resistance and relapse remain elusive. Although difficult to validate, it has been postulated that (I) relapse may be due to seeding from distant subclinical systemic malignant lymphocytes and not merely a regrowth of residual disease or (II) regrowth of PCNSL sub-clones that have inherent or acquired resistance to therapy, or that have found micro-environmental sanctuary behind the blood brain barrier (BBB) (18). The former hypothesis is potentially supported by preliminary reports demonstrating subclinical evidence of systemic disease by polymerase chain reaction of the rearranged immunoglobulin heavy-
chain genes; in the context of radiological CR (16,19,20). The latter hypothesis is better supported based on observations that suggest that relapse may present as a non-enhancing lesion (21–23) and that a majority of relapses occur at spatially distinct anatomical locations within the brain with previously intact BBB (16,17). In this review we outline potential therapeutic approaches and their relative merits, together with the numerous challenges inherent in treating patients with rrPCNSL.

**Relapsed vs. refractory PCNSL**

Most published clinical studies of rrPCNSL report data on heterogeneous cohorts of patients encompassing both relapsed (rel-PCNSL) and primary refractory (ref-PCNSL) disease. Although it is pragmatic to include both groups of patients together in clinical trials due to the rarity of the tumor, combining the two entities poses a risk of premature determination of futility in early phase studies due to the significant inherent difference in biology and clinical outcomes. Although there is a lack of consensus, some authors have used the term ref-PCNSL to refer to disease that progresses during first line HD-MTX-based therapy or within the first 6 months of an initial response, whilst rel-PCNSL describes disease relapse following a sustained period of CR after first line therapy (24). It is estimated that 10-15% of newly diagnosed PCNSL are refractory to HD-MTX based therapies and inherently have more aggressive disease (25,26).

In addition, patients with early recurrence may be inherently chemo-resistant unlike those that relapse much later. The risk of disease progression is influenced by a number of factors including: type of regimen used, dose-and time-intensity of treatment delivery, effectiveness of drug delivery to the CNS, drug resistance and inherent differences in tumor biology. It is rational to consider changing therapy to a non-MTX-based, non-cross resistant regimen for patients with ref-PCNSL under the assumption that these tumors are resistant to MTX. By contrast, ‘re-challenge’ with the same or similar MTX-based regimen is a reasonable approach in rel-PCNSL. Recognition and acknowledgement of the inherent differences between ref- and rel-PCNSL may allow a more efficient and accurate evaluation of efficacy when investigating novel approaches in the refractory or relapsed settings.

**Defining relapse or recurrence**

Most clinicians use radiologic criteria under the framework of the Report of an International Workshop to standardize baseline evaluation and response criteria for PCNSL to define relapse or recurrence (20). These criteria rely heavily on post gadolinium T1 weighted MRI brain imaging. This sequence is extremely sensitive in detecting disrupted BBB and contrast extravasation, but does not reliably reflect the true extent of disease. Indeed, autopsy studies provide convincing evidence to suggest that MRI significantly underestimates the burden of disease and that PCNSL is in fact a whole brain disease (27). Efforts to standardize and incorporate novel imaging techniques are being developed under the auspices of the International Primary Central Nervous System Lymphoma Collaborative Group (IPCG) (28). Incorporating MRI sequences such as diffusion weighted imaging, novel contrast agents such as ferumoxytol, and nuclear imaging, may further improve our ability to accurately assess the true disease burden, monitor response and facilitate early detection.
of relapse independent of the degree of BBB disruption (22,29). Thus, prospective validation of non-invasive predictive and prognostic biomarkers remains a priority. In this context, the endpoints to define the success of PCNSL therapy need to be more precisely defined. Criteria in clinical trials and routine practice frequently use objective overall response as an early indicator of efficacy. However, unlike other primary brain tumors, the value of partial response (PR) and stable disease (SD) is questionable in PCNSL. Data from observational studies suggest that subjects who attain CR have a significant survival advantage compared to those who do not (30,31). This is further supported by disappointingly low progression free survival (PFS) and overall survival (OS), even when high overall response rates (ORRs) are reported in prospective clinical studies evaluating rrPCNSL (Table 1) (30).

**Predicting the risk of relapse in PCNSL**

Identifying those patients at highest risk of early PCNSL progression or relapse remains somewhat imprecise, reliant on baseline clinical parameters that are insufficiently refined to allow stratification of treatment. A collaborative effort by The International Extranodal Lymphoma Study Group (IELSG) analyzed the prognostic role of patient-, lymphoma-, and treatment-related variables within a multicenter series of 378 PCNSL patients treated at 23 centers from five different countries. This analysis concluded that (I) Age >60 years, (II) performance status, (III) elevated lactate dehydrogenase (LDH) serum level, (IV) high CSF protein concentration, and (V) involvement of deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum) were significantly and independently associated with inferior survival (31). These data formed the IELSG prognostic score for patients treated with HD-MTX-based protocols. Overall survival estimates for those with a total score 0–1, 2–3 and >4, were 85%, 57% and 24% respectively.

However, an independent single institution (n=338) dataset from Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) concluded that age and performance status were the only variables independently associated with survival on multivariable analysis. In this study, recursive partitioning analysis (RPA) was used to create independent prognostic classes which were subsequently validated in three prospective PCNSL trial cohorts from the Radiation Therapy Oncology Group (RTOG) (32). The authors identified three distinct prognostic classes: class 1 (age <50 years), class 2 [age ≥50; Karnofsky performance score (KPS) ≥70] and class 3 (age ≥50; KPS <70) delineating significant differences in outcome with regard to both overall and failure-free survival. The simplicity and generalizability of the MSKCC scoring system is a potential advantage over the IELSG scoring system. However, there are very limited data about the validity of these scoring systems in the context of rrPCNSL. Notably, all existing prognostic models are based on clinical parameters measured at baseline; no robust data are yet available on dynamic factors measured during therapy and/or based on clinical, pathobiological or imaging characteristics of PCNSL (33–36). Identifying those most at risk of being refractory or relapse in PCNSL is further complicated by different first line regimens being employed in routine clinical practice (33).
Clinical challenges in the relapse/refractory setting

Key considerations when approaching the clinical problem of rrPCNSL include: what therapy/therapies the patient previously received, the quality of response to prior therapy, and duration of remission. The performance status of the patient together with a careful assessment of physiological fitness and consideration of neurocognitive dysfunction are equally important considerations when planning therapy. Whilst clinical trials should always be considered a priority for patients with rrPCNSL, suitable studies may not be accessible for many patients.

In routine clinical practice, the most commonly adopted treatment approaches, for sufficiently fit patients with rrPCNSL, include re-treatment with HD-MTX-based therapy or alternatively non-cross resistant chemotherapy with/without stem cell transplantation. Whole brain radiation therapy (WBRT) is also commonly employed for radiation-naïve patients with rrPCNSL. However, many patients with rrPCNSL are not good candidates for further intensive therapy for a number of reasons including: advanced age at relapse; impaired performance status; neurocognitive dysfunction; poor physiological fitness or co-morbid conditions. Moreover, the typically rapid decline in neurocognitive function, including impaired capacity to provide informed consent, together with the paucity of clinical trials in this setting presents a major challenge to the treating physicians and their patients. Here we review the published literature on rrPCNSL that may help guide therapeutic decisions.

Folate antimetabolites

Re-challenge with HD-MTX

HD-MTX is universally employed within treatment protocols for newly diagnosed PCNSL. Re-challenge with HD-MTX-based protocols is more likely to be efficacious in rel-PCNSL rather than in ref-PCNSL. A study evaluating 22 patients who were re-challenged with HD-MTX monotherapy (≥3 g/m^2), conferred an ORR of 91% to first salvage therapy with CR in 16 (73%) patients, 19 of whom had previously attained CR with first line HD-MTX. However, this was a very small retrospective study reported in 2004, prone to bias, and needs to be interpreted with caution (37). Moreover, the timing of relapse (early versus late) following first-line HD-MTX-based therapy is an important consideration when considering the value of re-challenge with HD-MTX. Another retrospective study evaluating 39 patients with rel-PCNSL after initially responding to HD-MTX reported an ORR of 85% and CR rate of 74%, although different regimens were used at MTX re-challenge [MPV and rituximab (44%) and MPV (23%), single-agent MTX (15%) and MTX, BCNU and etoposide (10%)]. Median PFS was 16 months, median OS 41 months and 1-year OS 79% (38). A more recent phase 1b study investigated HD-MTX with ibrutinib, followed by single-agent ibrutinib maintenance and is discussed later in this manuscript (14).

Pemetrexed

Pemetrexed is a folate antimetabolite chemically similar to MTX that targets both purine and pyrimidine metabolism. A prospective phase 1/2 trial which enrolled 27 subjects who received pemetrexed monotherapy, reported an ORR of 56% with 21% CR and 35% PR.
However, the median PFS was only 4.2 months (39). The dose expansion cohort of this study was terminated due to slow accrual after the primary objective of identifying the recommended maximum tolerated dose (900 mg/m$^2$ every 2 weeks) was achieved. A separate single arm prospective study that evaluated 17 subjects treated with pemetrexed at a dose of 900 mg/m$^2$ intravenous (i.v.) every 3 weeks reported a similar ORR of 59%, with a median OS of 7.8 months (40). Another single arm study evaluating 11 subjects with rrPCNSL at similar doses reported an ORR 55% (4 CR, 2 PR) with a median PFS was 5.7 months, and median OS was 10.1 months (9). Studies combining pemetrexed with rituximab (n=27), showed an ORR of 62.9% with CR in 22% (41). A smaller study (n=12) evaluating subjects over 65 who were deemed unlikely to tolerate HD-MTX described an ORR of 83% (4 CR, 6 PR) with a median OS of 19.5 months (42). The drug appeared to be generally well tolerated with modest hematological toxicities, infections, fatigue, rash and vomiting reported, but needs to be weighed in the context of patient characteristics, prior therapies and dose selected (9,42). Unlike HD-MTX, pemetrexed does not require hospitalization, but low-dose dexamethasone, folate, and B12 supplementation is recommended (9). These findings suggest that pemetrexed may have some efficacy in rrPCNSL but would require further evaluation in prospective studies prior to being adopted in routine practice.

Non-methotrexate-based chemotherapy approaches

Alkylating agents

It is estimated that nearly all systemically delivered large-molecule neurotherapeutics and more than 98% of all available small molecules do not achieve consistent therapeutic concentrations in the CNS (43). Even drugs such as Temozolomide (TMZ), a well-tolerated oral alkylating agent that has shown activity in other brain tumors, achieves CNS concentrations that are 20% less than their corresponding blood concentrations (44). A prospective phase 2 study (n=36) evaluating TMZ monotherapy in rrPCNSL showed an ORR of 31%, with 9 CR and 2 PR (7). A similar study in 17 heavily pretreated subjects reported 47% objective responses (5CR, 5 PR or SD) (45). However, the median OS remained short in both studies. Retrospective data of a combination of TMZ with rituximab (46–49), led to a multicenter phase 2 study of rituximab and TMZ in recurrent PCNSL but was prematurely terminated when futility was evident at interim analysis (11). Other combinations such as procarbazine, lomustine and vincristine (PCV) have been tested; the alkylating agent lomustine is known to achieve therapeutic concentrations across the neurovascular unit (NVU). Small retrospective studies evaluating PCV (n=7) report 4 CRs and 2 PRs with some long-term survivors (50). These findings suggest modest short-lived activity of alkylating agents in this setting.

Other cytotoxic chemotherapies and their combinations

Due to the lack of prospective data in the context of poor survival outcomes, a range of cytotoxic agents or their combinations, active in systemic lymphomas, have been utilized and retrospectively reported. A retrospective study, evaluating 14 patients who received high dose cytarabine (HD-AraC) as monotherapy, showed a modest response rate of only 35%. The responses were all PRs with no patients remaining free of progression over 6 months (median PFS 3 months) suggesting very limited efficacy of HD-AraC as monotherapy in
rrPCNSL (51). Similarly, other retrospective studies have assessed cytotoxic agents such as topotecan, bendamustine, gemcitabine and oxaliplatin that, in general, confer sub-optimal and short-lived responses (24,30).

A retrospective study reported the feasibility and activity of a combination of rituximab, ifosfamide and etoposide (R-IE regimen) in a multicenter series of rrPCNSL patients ≤5 years old (52). Patients in CR, PR or SD after the fourth course of R-IE were referred to WBRT or to high-dose chemotherapy supported by autologous stem cell transplant (HDT-ASCT) if previously irradiated. This study reports an ORR of 44% in 22 consecutive patients treated, with CR rate of 37% and 2 yr PFS of 21%.

A more recent prospective study from Fox et al. evaluated a dose-escalation schema to identify the recommended phase 2 dosing of thiotepa in combination with R-IE in an open label, phase 1/2 study for patients with r/r PCNSL (TIER study) (15). They report 52% ORR (14 out of 27 patients) with a CR/CRu rate of 33%; however, the median PFS was 3 months. These data describe the feasibility of TIER as a salvage regimen for r/r PCNSL but question its broader applicability, given the short PFS and OS times.

**High dose chemotherapy followed by autologous stem cell transplantation**

High dose chemotherapy (HDT) followed by ASCT is demonstrably effective and now widely employed as consolidation therapy for patients with newly diagnosed PCNSL and many modern upfront HD-MTX-based protocols are typically more intensive, and often include consolidation HDT-ASCT (1,25,26,53,54). For systemic DLBCL, HDT-ASCT is considered standard of care for eligible patients with relapsed/refractory disease who achieve remission with second-line multiagent chemotherapy (55). Two decades ago, early data emerged demonstrating the potential efficacy for patients with rrPCNSL. Based on promising retrospective data (56–58), a multicenter phase 2 study evaluating HDT with thiotepa, busulfan and cyclophosphamide (TBC) with ASCT demonstrated CR in 26 of the 27 patients evaluated. Of the 26 patients, 15 where chemosensitive and achieved an objective response (12 CR, 3 PR) to salvage HD cytarabine and etoposide while the remaining were chemorefractory (59). The median PFS was 11.6 months and 2-year PFS was 45% in the overall study population. Encouragingly, the median OS was not reached after a median follow up of 36 months in the chemosensitive group, while the median OS was 18.3 months for the chemorefractory group. More recently, a German cooperative group study for ASCT-eligible patients with rrPCNSL evaluated remission induction therapy with rituximab, HD-AraC and thiotepa followed by HDT-ASCT consolidation with rituximab/ Carmustine/thiotepa conditioning in 39 patients. In this phase 2 study, 56% of patients achieved CR after ASCT with an encouraging 2-year PFS of 46%, after a median follow up of 45 months (60). Inclusion of thiotepa in the conditioning regimen appears to be key; independently associated with improved outcomes (61,62). Although younger patients are more likely to be considered for HDT-ASCT approaches, a multicenter retrospective study supports this approach in appropriately selected older patients with rrPCNSL (median age: 67 yrs, range: 65–77 yrs) (63). Taken together, the published data support the role of HDT-ASCT consolidation for sufficiently fit patients with rrPCNSL who respond to second-line chemoimmunotherapy. The role of allogeneic transplantation remains experimental in
this setting, although small retrospective reports provide early indications of feasibility, including patients who have relapsed following previous HDT-ASCT (64–66).

**Approaches to enhance drug delivery across the neurovascular unit**

**Intra-arterial (IA) delivery after osmotic blood brain barrier disruption (BBBD)**

The NVU remains a key obstacle in efforts to improve treatment for brain tumors including PCNSL (67–69). In this context, intra-arterial (IA) delivery after osmotic BBBD is one example of an investigational approach. The opening of the tight junctions with a concentrated solution of mannitol allows increased levels of drugs (up to 100-fold) to reach the CNS as shown in preclinical and clinical studies (68). Phase 2 studies have demonstrated the effectiveness of HD MTX-based chemotherapy regimens delivered through osmotic BBBD without the use of consolidation WBRT and less associated neurotoxicity, at least in the newly diagnosed setting (70). Another multi-institution retrospective study evaluated non-MTX IA carboplatin-based chemotherapy with BBBD in 37 subjects with rrPCNSL (71). The authors describe the use of IA carboplatin and i.v. etoposide (n=16) or IA carboplatin, i.v. etoposide and i.v. cyclophosphamide (n=20). The authors reported 9 CR, 4 PR and 12 SD; a median OS of 6.8 months was reported with at least 6 of the patients surviving over 40 months at the time of publication. Of note, seizures (6−8%) noted with previous MTX-based IA/BBBD regimens were not seen with the carboplatin based regimen. In a more recent retrospective study from Finland, 19 (76%) of 25 patients treated with first or second line BBBD therapy achieved CR (72). Patients subsequently underwent ASCT consolidation resulting in two-year PFS and OS rates of 61% and 57% respectively and five-year OS of 47% with toxicities that appeared comparable to other approaches.

**Novel vascular targeting agents**

A more recent novel approach employed intravenous delivery of tumor necrosis factor-α coupled with NGR (NGR-hTNF), a peptide targeting CD13+ on the luminal side of CNS blood vessels to improve CNS bioavailability. In single arm phase 2 trial (INGRID study), Ferreri et al. used low-dose i.v. NGR-hTNF to enhance the delivery of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), a regimen frequently used and effective in systemic lymphomas but not effective by conventional delivery in PCNSL due to poor CNS bioavailability (73). Although there was no discernible increase in CSF levels of the R-CHOP agents, efficacy was attributed to the tumor specificity of NGR-hTNF in this single arm study with 9 of 12 patients with rrPCNSL achieving an objective response with 8 patients achieving CR.

**Targeted agents**

**Anti-CD20 agents**

Rituximab, an anti-CD20 monoclonal antibody has been increasingly employed in PCNSL treatment protocols given the CD20+ DLBCL histology and the established efficacy of rituximab when combined with chemotherapy for systemic DLBCL. Although some investigators question its potential utility due to its large molecular weight, it should be recognized that the NVU is dynamic and is neither permanently closed nor open.
Moreover, there are other influential factors including lipid solubility, plasma half-life and active transport mechanisms that impact drug delivery into the CNS. Pre-clinical data (74,75), together with data from retrospective clinical studies support the efficacy of single agent rituximab or in combination with other agents in PCNSL (8,10,76–83). The multicenter phase 2 IELSG32 study investigated three different induction chemotherapy regimens in a randomized fashion (arm A: HD-MTX plus HD-AraC; arm B: same as arm A plus rituximab; arm C: same as arm B plus thiotepa) (1). These data confirmed that the combination of an alkylating agent (thiotepa), two antimetabolites (methotrexate and cytarabine), and rituximab significantly improves outcome in terms of response rates, PFS and OS, although this study did not demonstrate a statistical difference between arm A and B (HD-MTX plus HD-AraC vs. HD-MTX plus HD-AraC plus rituximab). By contrast, a randomized phase 3 study (HOVON 105/ALLG NHL 24) did not find a benefit for rituximab in the context of a different chemotherapy backbone, without HDT-ASCT consolidation (84). Subsequently, the trial-level data from the two randomized studies were pooled and analyzed as a meta-analysis (a total of 343 patients); Schmitt et al. conclude that rituximab in combination with MTX-based chemotherapy improves PFS in newly diagnosed PCNSL, but evidence for an OS benefit was not forthcoming from this analysis (85). In addition to rituximab’s role in targeting CD20, emerging evidence suggests that it may also play an adjuvant immunomodulatory role (86,87).

**Bruton’s tyrosine kinase inhibitors**

Ibrutinib is a first-in-class orally administered inhibitor of Bruton’s tyrosine kinase (BTK). A single arm multicenter phase 2 study of ibrutinib monotherapy (n=52) described objective responses in 27 patients (52%) including 10 (19%) CRs. Notwithstanding high rates of response, the median PFS was short at 3.3 months (95% CI, 2–6.4) (88,89). Ibrutinib has also been investigated in combination with chemotherapy. A small phase 1 study (n=18, 5 untreated, 13 rrPCNSL) initially undertook dose-finding of ibrutinib monotherapy for 14 days within a window study design, prior to combining ibrutinib with a non-MTX-based multiagent chemoimmunotherapy regimen termed TEDDi-R (TMZ, etoposide, liposomal doxorubicin, dexamethasone, and rituximab), 86% of evaluable patients achieved CR with 67% remaining disease free at 2 years (90). Another phase 1b study investigated the sequential combination of ibrutinib (560 or 840 mg daily dosing) with HD-MTX and rituximab in patients with rel/ref CNS lymphoma (9 PCNSL and 6 systemic lymphoma with CNS involvement) reported an objective response in 80% (12 out of 15 subjects); with an overall median PFS of 9.2 months (13,14). More recently, a phase 1/2 study reported by Narita et al. evaluated Tirabrutinib, a second-generation, selective, irreversible oral BTK inhibitor in rrPCNSL (91). Amongst 44 patients treated, the ORR was 64%. Clinical response was reported at each dose level and includes 5 CR/CRu at 320 mg, 100.0% (7/7 patients) with 4 CR/CRu at 480 mg, and 52.9% (9/17 patients) with 6 CR/CRu at 480 mg under fasted conditions. These findings are consistent with the ibrutinib data; despite high rates of response, the median PFS was disappointingly short at 2.9 months. Complete resistance to ibrutinib is associated with missense mutation within the coiled-coil domain of CARD11, other mutations such as CD79b that is frequently associated with MYD88 mutations, inactivating lesions in TNFAIP3, a negative regulator of NF-κB were reported in those with incomplete response to ibrutinib (30,92,93). Grommes et al. also reported that
patients with concurrent mutations in MYD88 and CD79b, failed to achieve CR (30). It is noted that the CSF/plasma concentration ratio of tirabrutinib was approximately 13–18%, which is higher than the published ratio of ibrutinib (30,91). These important findings may help develop strategies to overcome resistance and improve durations of response.

Timing of BTK inhibitors with respect to food may also have important clinical implications. For example, Ibrutinib administered in fasted conditions reduced blood levels to approximately 60% as compared with dosing in proximity to food-intake, regardless of timing or type of meal (94). Similarly, BTK inhibitors impair the innate immune response and increases the risk of serious opportunistic fungal infections such as Aspergillus fumigatus and pneumocystis jirovecii (13,91). This may be particularly significant in the setting of rrPCNSL where patients are frequently older, heavily pretreated and on high doses of steroids for neurological symptom management.

**Mammalian target of rapamycin (mTOR) inhibitors**

Preclinical and clinical evidence suggested that the PI3K/AKT/mTOR pathway may play a relevant role in the biology of aggressive B cell lymphomas. A phase 2 study of the mTOR inhibitor Temsirolimus for patients with rrPCNSL, reported an objective response in 54% but the responses were very short lived (PFS 2.1 months) with considerable treatment associated mortality (13.5%) (12). Notably, in 14 paired blood/CSF samples, there was negligible evidence of temsirolimus in the CSF.

**Immunomodulatory approaches**

**IMiDs**

Immunomodulatory therapies have had a significant impact within the blood cancer field, including activity in B cell lymphoproliferative disease (95). Prior dogma of the CNS being an ‘immune privileged’ sanctuary site has been challenged. Oral immunomodulatory agents (IMiDs) lenalidomide and pomalidomide have the ability to exert direct cytotoxic effects on the tumor, in addition to potentially beneficial effects mediated through immune-effector cells within the tumor micro-environment. These agents bind cereblon and downregulate IRF4 that are, in turn, direct targets of NF-κB transcription factors induced by B cell receptor (BCR) signaling that is frequently deregulated in PCNSL (96,97). In a phase 1 study (n=14) of lenalidomide in rrPCNSL and systemic CNSL, 3 patients achieved CR, with a suggestion of slightly better outcomes in systemic CNSL (2 CRs) compared to 1 CR in the PCNSL cohort (98,99). The ORR to lenalidomide monotherapy was 64%, with 4 patients having a sustained response for over 18 months. A multicenter phase 2 study using lenalidomide and rituximab followed by lenalidomide monotherapy as ‘maintenance’ for responders, enrolled 50 patients with rrPCNSL. The ORR for the whole study was 48% with CR reported in 13 (29%) patients. The median PFS was 7.8 months with no evidence of a plateau in the survival curves (100). Similarly, a phase 1 study of pomalidomide treated in combination with dexamethasone followed by pomalidomide monotherapy, of the 25 evaluable subjects, 8 (32%) attained CR with a median PFS of 5.3 months (101).
Immune check point inhibitors

The biological implications and prognostic significance of the rich T-cell infiltration in the tumor microenvironment of PCNSL has not been elucidated, but may permit opportunities for therapeutic manipulation. Programmed death ligand (PD-L1) and its corresponding cell surface receptor protein (PD-1) belong to a class of proteins termed immune check points. Their interactions are thought to be important for many tumors, including B cell lymphomas, to evade T cell mediated anti-tumor immunity (102). A small study (n=20) reported that PD1 and PD-L1 overexpression was demonstrable in the vast majority of PCNSL tissue biopsies studied (103). Moreover, PCNSL commonly displays alterations of chromosome 9p24.1, a genetic mechanism that facilitates PD-1 mediated T-cell immune evasion (86). Comprehensive characterization using combined genetic and immunohistochemistry analyses demonstrated that PCNSL frequently exhibits 9p24.1/PD-L1/PD-L2 copy number alterations and translocations; suggesting a genetic basis of potential immune evasion mechanisms. Thus, immune checkpoint inhibitors have been investigated in PCNSL (104). An initial retrospective report of 4 patients treated with the PD1 inhibitor nivolumab reported promising evidence of activity in rrPCNSL. All 4 patients responded with 3 achieving CR although interpretation of efficacy was confounded by additional therapies (e.g., WBRT) for some patients (105). A retrospective series of six heavily pre-treated patients who received PD-1 inhibitor therapy in combination with rituximab showed an ORR of 50% (3 CR) (87). These observations warrant prospective evaluation in clinical trials. NCT02857426 is evaluating whether nivolumab is effective in the treatment of rrPCNSL and relapsed/refractory primary testicular lymphoma (PTL); results are awaited. Notably, emerging evidence suggest that malignant B-cells may express factors including IL-4, IL-10, and metabolites such as lactate and kynurenine that can facilitate an immunosuppressive tumor microenvironment, in addition to deregulated PD1, PD-L1/L2 pathways, further contributing to an immunosuppressive microenvironment and potentially diminishing the efficacy of check point inhibitors in PCNSL (86).

Chimeric antigen receptor (CAR) T-cell therapy

CD19-directed chimeric antigen receptor (CAR) T-cell therapies have demonstrated remarkable efficacy in relapsed/refractory systemic DLBCL (106,107). The implications of this paradigm shift in the therapy of rrDLBCL opens up many questions and opportunities for the treatment of CNS lymphoma, including rrPCNSL (108–110). Early reports suggest that CD19-directed CAR-T cell therapies may be effective for some patients with CNS involvement by DLBCL (110,111). Importantly, the potential for severe CNS toxicities from CD19-directed CAR T cell therapy requires diligent study for patients with PCNSL given the disrupted BBB and often pre-existing neurocognitive dysfunction. Nevertheless, this is a therapeutic area of potential promise for patients with rrPCNSL (112) and dedicated prospective studies are underway; NCT04443829 is currently enrolling adults (age ≥16) with rrPCNSL.

Conclusion

Despite substantial therapeutic progress in the treatment of PCNSL, relapsed and refractory disease remains a relatively common scenario and a major area of unmet clinical need. Most
patients with rrPCNSL do not achieve a durable second remission and will succumb to their disease, often within months of initial disease progression. rrPCNSL presents a number of unique challenges that continue to hamper therapeutic progress, notably: insufficient understanding of disease pathobiology (due in part to difficulties accessing tumor material) and mechanisms of treatment failure, together with the clinical challenges of neurocognitive dysfunction and impairment of performance status. The heterogeneity of rrPCNSL, manifest clinically by response quality and duration of remission to previous therapy(ies), is a key consideration when considering further therapeutic options and designing clinical studies. Conventional therapies including re-treatment with HD-MTX-based regimens, HDT-ASCT consolidation and radiation therapy, remain important standard treatment options for rrPCNSL. However, there is much interest in a range of emerging novel therapeutics, including both targeted agents and immunotherapies. Optimizing delivery of therapy to the CNS with renewed attention to negotiating the BBB also remains a key priority. Given the short duration of responses to both conventional and novel therapies, the major challenge for the field is to effectively consolidate and prolong responses in the setting of rrPCNSL. This may be achieved by incorporating rationally selected agents with distinct non-overlapping modes of action, and/or by applying novel consolidation/maintenance approaches. Further progress in rrPCNSL will require close collaboration both within and between disciplines to facilitate a deeper understanding of PCNSL pathobiology, together with improved technologies to measure and monitor response to therapy and improve risk stratification. Therapeutic progress in rrPCNSL requires a broader and more nuanced portfolio of carefully designed clinical trials to maximize opportunities, to both learn from our patients and deliver for them improved treatment outcomes and long-term survival.

Acknowledgments

The authors would like to thank Amy Huddleston, Sofia Gallamore and Heather Leon for their administrative support.

Funding

This work was supported by the Jonathan D. Lewis Foundation to PA and NDD, and by Cancer Research UK, Blood Cancer UK (Grant ID: 13069), and Cure Leukaemia UK to CPF.

References

1. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016; 3: e217–27. [PubMed: 27132696]
2. Korfel A, Schlegel U. Diagnosis and treatment of primary CNS lymphoma. Nat Rev Neurol. 2013; 9: 317–27. [PubMed: 23670107]
3. von Baumgarten L, Illerhaus G, Korfel A, et al. The Diagnosis and Treatment of Primary CNS Lymphoma. Dtsch Arztebl Int. 2018; 115: 419–26. [PubMed: 29999484]
4. Nayak L, Hedvat C, Rosenblum MK, et al. Late relapse in primary central nervous system lymphoma: clonal persistence. Neuro Oncol. 2011; 13: 525–9. [PubMed: 21372070]
5. Yamanaka R, Morii K, Shinbo Y, et al. Late relapse of primary central nervous system lymphoma. Leuk Lymphoma. 2017; 58: 475–7. [PubMed: 27397141]
6. Calimeri T, Lopedote P, Ferreri AJM. Risk stratification and management algorithms for patients with diffuse large B-cell lymphoma and CNS involvement. Ann Lymphoma. 2019; 3: 7.
7. Reni M, Zaja F, Mason W, et al. Temozolomide as salvage treatment in primary brain lymphomas. Br J Cancer. 2007; 96: 864–7. [PubMed: 17325700]

8. Batchelor TT, Grossman SA, Mikkelsen T, et al. Rituximab monotherapy for patients with recurrent primary CNS lymphoma. Neurology. 2011; 76: 929–30. [PubMed: 21383311]

9. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. Cancer. 2012; 118: 3743–8. [PubMed: 22179954]

10. Rubenstein JL, Li J, Chen L, et al. Multicenter phase 1 trial of intraventricular immunochemotherapy in recurrent CNS lymphoma. Blood. 2013; 121: 745–51. [PubMed: 23197589]

11. Nayak L, Abrey LE, Drappatz J, et al. Multicenter phase II study of rituximab and temozolomide in recurrent primary central nervous system lymphoma. Leuk Lymphoma. 2013; 54: 58–61. [PubMed: 22656234]

12. Korf F, Schlegel U, Herrlinger U, et al. Phase II Trial of Temsirolimus for Relapsed/Refractory Primary CNS Lymphoma. J Clin Oncol. 2016; 34: 1757–63. [PubMed: 26976424]

13. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma. Cancer Discov. 2017; 7: 1018–29. [PubMed: 28619981]

14. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. Blood. 2019; 133: 436–45. [PubMed: 30567753]

15. Fox CP, Ali AS, Auer D, et al. A Phase I/II Dose-Escalation Study of Thiotaepa-Based Immunochemotherapy in Relapsed/Refractory Primary Central Nervous System Lymphoma; The Tier Trial. Blood. 2019; 134: 2879.

16. Ambady P, Fu R, Netto JP, et al. Patterns of relapse in primary central nervous system lymphoma: inferences regarding the role of the neuro-vascular unit and monoclonal antibodies in treating occult CNS disease. Fluids Barriers CNS. 2017; 14: 16. [PubMed: 28577579]

17. Patel MP, Kirkpatrick JP, Johnson MO, et al. Patterns of relapse after successful completion of initial therapy in primary central nervous system lymphoma: a case series. J Neurooncol. 2020; 147: 477–83. [PubMed: 32140975]

18. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? Neurology. 2002; 59: 1557–62. [PubMed: 12451197]

19. Jahnke K, Hummel M, Korf F, et al. Detection of subclinical systemic disease in primary CNS lymphoma by polymerase chain reaction of the rearranged immunoglobulin heavy-chain genes. J Clin Oncol. 2006; 24: 4754–7. [PubMed: 16966685]

20. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 2005; 23: 5034–43. [PubMed: 15959902]

21. Chen H, Dong H. A rare case of nonenhancing primary central nervous system lymphoma mimic multiple sclerosis. Neurosciences (Riyadh). 2015; 20: 380–4. [PubMed: 26492120]

22. Chiavazza C, Pellerino A, Ferrio F, et al. Primary CNS Lymphomas: Challenges in Diagnosis and Monitoring. Biomed Res Int. 2018; 2018 3606970 [PubMed: 30035121]

23. Bowden SG, Munger DN, Thiessen J, et al. The clinical heterogeneity of entirely nonenhancing CNS lymphoma: a case series. CNS Oncol. 2021; 10 CNS67 [PubMed: 33329424]

24. Holdhoff M, Wagner-Johnston N, Roschewski M. Systemic Approach to Recurrent Primary CNS Lymphoma: Perspective on Current and Emerging Treatment Strategies. Onco Targets Ther. 2020; 13: 8323–35. [PubMed: 32903865]

25. Ferreri AJM, Czyzewska K, Pulczynski E, et al. Wholebrain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemioimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017; 4: e510–23. [PubMed: 29054815]

26. Houllier C, Taillandier L, Dureau S, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. J Clin Oncol. 2019; 37: 823–33. [PubMed: 30785830]
27. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? Neurology. 2002; 59: 1557–62. [PubMed: 12451197]

28. Barajas RF, Politi LS, Anzalone N, et al. Consensus recommendations for MRI and PET imaging of primary central nervous system lymphoma: guideline statement from the International Primary CNS Lymphoma Collaborative Group (IPCG). Neuro Oncol. 2021; 23: 1056–71. [PubMed: 33560416]

29. Farrell BT, Hamilton BE, Dósa E, et al. Using iron oxide nanoparticles to diagnose CNS inflammatory diseases and PCNSL. Neurology. 2013; 81: 256–63. [PubMed: 23771486]

30. Grommes C, DeAngelis LM. Primary CNS Lymphoma. J Clin Oncol. 2017; 35: 2410–8. [PubMed: 28640701]

31. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003; 21: 266–72. [PubMed: 12525518]

32. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol. 2006; 24: 5711–5. [PubMed: 1716938]

33. Biccler JL, Savage KJ, Brown PDN, et al. Risk of death, relapse or progression, and loss of life expectancy at different progression-free survival milestones in primary central nervous system lymphoma. Leuk Lymphoma. 2019; 60: 2516–23. [PubMed: 30943052]

34. Cambruzzi E. Primary Intra-Axial Diffuse Large B-Cell Lymphoma in Immunocompetent Patients: Clinical Impact of Molecular Analysis and Histogenetic Evaluation. World Neurosurg. 2020; 134: 215–20. [PubMed: 31605845]

35. Nosrati A, Monabati A, Sadeghipour A, et al. MYC, BCL2, and BCL6 rearrangements in primary central nervous system lymphoma of large B cell type. Ann Hematol. 2019; 98: 169–73. [PubMed: 30306208]

36. Luo Q, Yang C, Fu C, et al. Prognostic Role of Blood Markers in Primary Central Nervous System Lymphoma Patients Treated With High-Dose Methotrexate-Based Therapy. Front Oncol. 2021; 11 639644 [PubMed: 33965552]

37. Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. Clin Cancer Res. 2004; 10: 5643–6. [PubMed: 15355887]

38. Pentsova E, Deangelis LM, Omuro A. Methotrexate rechallenge for recurrent primary central nervous system lymphoma. J Neurooncol. 2014; 117: 161–5. [PubMed: 24481997]

39. Dietrich J, Versmee L, Drappatz J, et al. Pemetrexed in Recurrent or Progressive Central Nervous System Lymphoma: A Phase I Multicenter Clinical Trial. Oncologist. 2020; 25: 747. e1273 [PubMed: 32520407]

40. Sun Y, Wang Y, Han S, et al. Efficacy and safety of pemetrexed on recurrent primary central nervous system lymphomas in China: a prospective study. Onco Targets Ther. 2017; 10: 2595–600. [PubMed: 28553124]

41. Zhao HT, Chen J, Shi SB, et al. Pemetrexed plus rituximab as second-line treatment for primary central nervous system lymphoma. Med Oncol. 2015; 32: 351. [PubMed: 25428379]

42. Han S, Wang M, Liu B, et al. Pemetrexed for primary central nervous system lymphoma in the elderly. Clin Transl Oncol. 2016; 18: 138–43. [PubMed: 26169215]

43. Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Comb Chem. 1999; 1: 55–68. [PubMed: 10746014]

44. Naidoo J, Panday H, Jackson S, et al. Optimizing the Delivery of Antineoplastic Therapies to the Central Nervous System. Oncology (Williston Park). 2016; 30: 953–62. [PubMed: 27854097]

45. Makino K, Nakamura H, Hide T, et al. Salvage treatment with temozolomide in refractory or relapsed primary central nervous system lymphoma and assessment of the MGMT status. J Neurooncol. 2012; 106: 155–60. [PubMed: 21720808]

46. Pitini V, Arrigo C, Righi M. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. Cancer. 2004; 101: 2900–1. [PubMed: 15529311]

47. Wong ET, Tishler R, Barron L, et al. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. Cancer. 2004; 101: 139–45. [PubMed: 15221999]
48. Wong ET. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. Neurology. 2005; 64: 934. [PubMed: 15753455]

49. Enting RH, Demopoulos A, DeAngelis LM, et al. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. Neurology. 2004; 63: 901–3. [PubMed: 15365145]

50. Herrlinger U, Brugger W, Bamberg M, et al. PCV salvage chemotherapy for recurrent primary CNS lymphoma. Neurology. 2000; 54: 1707–8. [PubMed: 10762527]

51. Chamberlain MC. High-dose cytarabine salvage therapy for recurrent primary CNS lymphoma. J Neurooncol. 2016; 126: 545–50. [PubMed: 23161567]

52. Mappa S, Marturano E, Licata G, et al. Salvage chemoimmunotherapy with rituximab, ifosfamide and etoposide (R-IE regimen) in patients with primary CNS lymphoma relapsed or refractory to high-dose methotrexate-based chemotherapy. Hematol Oncol. 2013; 31: 143–50. [PubMed: 23161567]

53. Schorb E, Fox CP, Kasenda B, et al. Induction therapy with the MATRix regimen in patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system - an international study of feasibility and efficacy in routine clinical practice. Br J Haematol. 2020; 189: 879–87. [PubMed: 31997308]

54. Schorb E, Finke J, Ihorst G, et al. Age-adjusted high-dose chemotherapy and autologous stem cell transplant in elderly and fit primary CNS lymphoma patients. BMC Cancer. 2019; 19: 287. [PubMed: 30925912]

55. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med. 2021; 384: 842–58. [PubMed: 33657296]

56. Soussain C, Hoang-Xuan K, Levy V. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. Bull Cancer. 2004; 91: 189–92. [PubMed: 15047459]

57. Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by hematopoietic stemcell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol. 2001; 19: 742–9. [PubMed: 11157026]

58. Welch MR, Sauter CS, Matasar MJ, et al. Autologous stem cell transplant in recurrent or refractory primary or secondary central nervous system lymphoma using thiotepa, busulfan and cyclophosphamide. Leuk Lymphoma. 2015; 56: 361–7. [PubMed: 24745937]

59. Soussain C, Hoang-Xuan K, Taillandier L, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. J Clin Oncol. 2008; 26: 2512–8.

60. Kasenda B, Ihorst G, Schroers R, et al. High-dose chemotherapy with autologous haematopoietic stem cell support for relapsed or refractory primary CNS lymphoma: a prospective multicentre trial by the German Cooperative PCNSL study group. Leukemia. 2017; 31: 2623–9. [PubMed: 28559537]

61. Scordo M, Wang TP, Ahn KW, et al. Outcomes Associated With Thiotepa-Based Conditioning in Patients With Primary Central Nervous System Lymphoma After Autologous Hematopoietic Cell Transplant. JAMA Oncol. 2021; 7: 993–1003. [PubMed: 33956047]

62. Kondo E, Ikeda T, Izutsu K, et al. High-Dose Chemotherapy with Autologous Stem Cell Transplantation in Primary Central Nervous System Lymphoma: Data From the Japan Society for Hematopoietic Cell Transplantation Registry. Biol Blood Marrow Transplant. 2019; 25: 899–905. [PubMed: 30664936]

63. Schorb E, Fox CP, Fritsch K, et al. High-dose thiotepa-based chemotherapy with autologous stem cell support in elderly patients with primary central nervous system lymphoma: a European retrospective study. Bone Marrow Transplant. 2017; 52: 1113–9. [PubMed: 28436974]

64. Mika T, Ladigan S, Baraniskin A, et al. Allogeneic hematopoietic stem cell transplantation for primary central nervous system lymphoma. Haematologica. 2020; 105: e160–3. [PubMed: 31399528]
65. Varadi G, Or R, Kapelushnik J, et al. Graft-versus-lymphoma effect after allogeneic peripheral blood stem cell transplantation for primary central nervous system lymphoma. Leuk Lymphoma. 1999; 34: 185–90. [PubMed: 10350348]

66. Atilla E, Sahin U, Atilla PA, et al. Allogeneic stem cell transplantation for relapsed primary central nervous system lymphoma: Is it feasible? Hematol Oncol Stem Cell Ther. 2019; 12: 220–5. [PubMed: 29559300]

67. Neuwelt E, Ambady P, Muldoon L, et al. Outwitting the Blood-Brain Barrier. Oncology (Williston Park). 2016; 30: 963–966. [PubMed: 27854098]

68. Neuwelt EA, Brummett RE, Doolittle ND, et al. First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. J Pharmacol Exp Ther. 1998; 286: 77–84. [PubMed: 9655844]

69. Blakeley JO, Olson J, Grossman SA, et al. Effect of blood brain barrier permeability in recurrent high grade gliomas on the intratumoral pharmacokinetics of methotrexate: a microdialysis study. J Neurooncol. 2009; 91: 51–8. [PubMed: 18787762]

70. Doolittle ND, Dósa E, Fu R, et al. Preservation of cognitive function in primary CNS lymphoma survivors a median of 12 years after enhanced chemotherapy delivery. J Clin Oncol. 2013; 31: 4026–7. [PubMed: 24101051]

71. Tyson RM, Siegal T, Doolittle ND, et al. Current status and future of relapsed primary central nervous system lymphoma (PCNSL). Leuk Lymphoma. 2003; 44: 627–33. [PubMed: 12769339]

72. Kuitunen H, Tokola S, Siniluoto T, et al. Promising treatment results with blood brain barrier disruption (BBBD) based immunochemotherapy combined with autologous stem cell transplantation (ASCT) in patients with primary central nervous system lymphoma (PCNSL). J Neurooncol. 2017; 131: 293–300. [PubMed: 27752883]

73. Ferreri AJM, Calimeri T, Conte GM, et al. R-CHOP preceded by blood-brain barrier permeabilization with engineered tumor necrosis factor-α in primary CNS lymphoma. Blood. 2019; 134: 252–62. [PubMed: 31118164]

74. Muldoon LL, Lewin SJ, Dósa E, et al. Imaging and therapy with rituximab anti-CD20 immunotherapy in an animal model of central nervous system lymphoma. Clin Cancer Res. 2011; 17: 2207–15. [PubMed: 21385922]

75. Maza S, Kiewe P, Munz DL, et al. First report on a prospective trial with yttrium-90-labeled ibritumomab tiuxetan (Zevalin) in primary CNS lymphoma. Neuro Oncol. 2009; 11: 423–9. [PubMed: 19060176]

76. Holdhoff M, Ambady P, Abdelaziz A, et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology. 2014; 83: 235–9. [PubMed: 24928128]

77. Birnbaum T, Stadler EA, von Baumgarten L, et al. Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. J Neurooncol. 2012; 109: 285–91. [PubMed: 22570142]

78. Mocikova H, Pytlik R, Sykorova A, et al. Role of rituximab in treatment of patients with primary central nervous system lymphoma: a retrospective analysis of the Czech lymphoma study group registry. Leuk Lymphoma. 2016; 57: 2777–83. [PubMed: 27087066]

79. Houllier C, Ghesquières H, Chabrot C, et al. Rituximab, methotrexate, procarbazine, vincristine and intensified cytarabine consolidation for primary central nervous system lymphoma (PCNSL) in the elderly: a LOC network study. J Neurooncol. 2017; 133: 315–20. [PubMed: 28432587]

80. Miyakita Y, Ohno M, Takahashi M, et al. Immunochemotherapy using rituximab (RTX) and high-dose methotrexate (HD-MTX): an evaluation of the addition of RTX to HD-MTX in recurrent primary central nervous system lymphoma (PCNSL). Jpn J Clin Oncol. 2017; 47: 919–24. [PubMed: 28981729]

81. Ly KL, Crew LL, Graham CA, et al. Primary central nervous system lymphoma treated with high-dose methotrexate and rituximab: A single-institution experience. Oncol Lett. 2016; 11: 3471–6. [PubMed: 27123138]

82. Kansara R, Shenkier TN, Connors JM, et al. Rituximab with high-dose methotrexate in primary central nervous system lymphoma. Am J Hematol. 2015; 90: 1149–54. [PubMed: 26414492]
83. Lai GG, Koo YX, Tao M, et al. Use of rituximab in combination with high-dose methotrexate in the treatment of primary central nervous system lymphoma in a mycophenolate mofetil treated patient with lupus nephritis. Acta Oncol. 2011; 50: 144–5. [PubMed: 20670084]

84. Bromberg JEC, Issa S, Bakunina K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2019; 20: 216–28. [PubMed: 30630772]

85. Schmitt AM, Herbrand AK, Fox CP, et al. Rituximab in primary central nervous system lymphoma-A systematic review and meta-analysis. Hematol Oncol. 2019; 37: 548–57. [PubMed: 31418878]

86. Rubenstein JL. Can rituximab unlock the innate potential of checkpoint blockade in the CNS? Leuk Lymphoma. 2019; 60: 281–3. [PubMed: 30188237]

87. Ambady P, Szidonya L, Firkins J, et al. Combination immunotherapy as a non-chemotherapy alternative for refractory or recurrent CNS lymphoma. Leuk Lymphoma. 2019; 60: 515–8. [PubMed: 30033836]

88. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II ‘proof-of-concept’ iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. Eur J Cancer. 2019; 117: 121–30. [PubMed: 31279304]

89. Houillier C, Soussain C, Ghesquières H, et al. Management and outcome of primary CNS lymphoma in the modern era: An LOC network study. Neurology. 2020; 94: e1027–39. [PubMed: 31907289]

90. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma. Cancer Cell. 2017; 31: 833–843. e5 [PubMed: 28552327]

91. Narita Y, Nagane M, Mishima K, et al. Phase I/II study of tirabrutinib, a second-generation Bruton’s tyrosine kinase inhibitor, in relapsed/refractory primary central nervous system lymphoma. Neuro Oncol. 2021; 23: 122–33. [PubMed: 32583848]

92. Wu C, de Miranda NF, Chen L, et al. Genetic heterogeneity in primary and relapsed mantle cell lymphomas: Impact of recurrent CARD11 mutations. Oncotarget. 2016; 7: 38180–90. [PubMed: 27224912]

93. Kim JH, Kim WS, Ryu K, et al. CD79B limits response of diffuse large B cell lymphoma to ibrutinib. Leuk Lymphoma. 2016; 57: 1413–22. [PubMed: 26699656]

94. de Jong J, Sukbuntherng J, Skee D, et al. The effect of food on the pharmacokinetics of oral ibrutinib in healthy participants and patients with chronic lymphocytic leukemia. Cancer Chemother Pharmacol. 2015; 75: 907–16. [PubMed: 25724156]

95. Khalil DN, Smith E, Brentjens R, et al. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Review Nat Rev Clin Oncol. 2016; 13: 273–90. [PubMed: 26977780]

96. Zhang LH, Kosek J, Wang M, et al. Lenalidomide efficacy in activated B-cell-like subtype diffuse large B-cell lymphoma is dependent upon IRF4 and cereblon expression. Br J Haematol. 2013; 160: 487–502. [PubMed: 23252516]

97. Camilleri-Brot P, Crinière E, Brot P, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. Blood. 2006; 107: 190–6. [PubMed: 16150948]

98. Rubenstein JL, Geng H, Fraser EJ, et al. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. Blood Adv. 2018; 2: 1595–607. [PubMed: 29986852]

99. Houillier C, Choquet S, Touitou V, et al. Lenalidomide monotherapy as salvage treatment for recurrent primary CNS lymphoma. Neurology. 2015; 84: 325–6. [PubMed: 25527263]

100. Ghesquières H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRi) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective ‘proof of concept’ phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†. Ann Oncol. 2019; 30: 621–8. [PubMed: 30698644]
101. Tun HW, Johnston PB, DeAngelis LM, et al. Phase 1 study of pomalidomide and dexamethasone for relapsed/refractory primary CNS or vitreoretinal lymphoma. Blood. 2018; 132: 2240–8. [PubMed: 30262659]

102. Andorsky DJ, Yamada RE, Said J, et al. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res. 2011; 17: 4232–44. [PubMed: 21540239]

103. Berghoff AS, Ricken G, Widhalm G, et al. PD1 (CD279) and PD-L1 (CD274, B7H1) expression in primary central nervous system lymphomas (PCNSL). Clin Neuropathol. 2014; 33: 42–9. [PubMed: 24359606]

104. Chapuy B, Roemer MG, Stewart C, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. Blood. 2016; 127: 869–81. [PubMed: 26702065]

105. Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood. 2017; 129: 3071–3. [PubMed: 28356247]

106. Doraiswamy A, Shah MR, Bannerji R. Immunotherapies Old and New: Hematopoietic Stem Cell Transplant, Chimeric Antigen Receptor T Cells, and Bispecific Antibodies for the Treatment of Relapsed/Refractory Diffuse Large B Cell Lymphoma. Curr Hematol Malig Rep. 2021; 16: 72–81. [PubMed: 33619641]

107. Al-Mansour M, Al-Foheidi M, Ibrahim E. Efficacy and safety of second-generation CAR T-cell therapy in diffuse large B-cell lymphoma: A meta-analysis. Mol Clin Oncol. 2020; 13: 33.

108. Tiberghien P, Deconinck E, Adotevi O. More on Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma. N Engl J Med. 2017; 377: 2101–2.

109. Abramson JS, Chen YB. More on Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma. N Engl J Med. 2017; 377: 2102. [PubMed: 29166240]

110. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019; 134: 860–6. [PubMed: 31320380]

111. Tu S, Zhou X, Guo Z, et al. CD19 and CD70 Dual-Target Chimeric Antigen Receptor T-Cell Therapy for the Treatment of Relapsed and Refractory Primary Central Nervous System Diffuse Large B-Cell Lymphoma. Front Oncol. 2019; 9: 1350. [PubMed: 31867275]

112. Li T, Zhao L, Zhang Y, et al. CAR T-Cell Therapy Is Effective but Not Long-Lasting in B-Cell Lymphoma of the Brain. Front Oncol. 2020; 10: 1306. [PubMed: 32903866]
Table 1
Summary of selected prospective clinical trials investigating activity in refractory/relapsed PCNSL

| First author | Year | Agents                                      | ORR/n [%] | CR [%] | Median PFS (months) |
|--------------|------|---------------------------------------------|-----------|--------|---------------------|
| Reni (7)     | 2007 | Temozolomide                                | 11/36 [31]| 9 [25] | 2.8                 |
| Batchelor (8)| 2011 | Rituximab                                   | 5/12 [42] | 3 [25] | 1.9                 |
| Raizer (9)   | 2012 | Pemetrexed                                  | 6/11 [55] | 4 [36] | 5.7                 |
| Rubenstein (10)| 2013| Intrathecal (rituximab + Methotrexate)  | 6/14 [43] | 2 [14] | 1.2                 |
| Nayak (11)   | 2013 | Rituximab + Temozolomide + Prednisone       | 5/14 [36] | 2 [14] | 1.6                 |
| Korfel (12)  | 2016 | Temsirolimus                                 | 20/37 [54]| 8 [21] | 2.1                 |
| Grommes (13) | 2017 | Ibrutinib                                   | 15/20 [75] | 8 [53] | 5.5                 |
| Grommes (14) | 2019 | HD-MTX + Rituximab + Ibrutinib              | 12/15 [80]| 8 [53] | 9.2                 |
| Fox (15)     | 2019 | ‘TIER’ Thiotepa + Ifosfamide + Etoposide + Rituximab | 14/27 [52]| 9 [33] | 3                  |

PCNSL, primary central nervous system lymphoma.