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Lymphoma (JL Muñoz, Section Editor)

Central Nervous System Lymphoma: Novel Therapies

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Opinion statement

Primary central nervous system lymphomas (PCNSLs) are very rare neoplasms and continue to be challenging to treat. While high-dose methotrexate (HD-MTX)-based regimens are the currently accepted standard first-line therapy for newly diagnosed patients, the optimal induction therapies are still unknown. The role of consolidation therapies continues to evolve with a variety of chemotherapy regimens, including high-dose chemotherapy with stem cell rescue and reduced or deferred whole brain radiotherapy being used. Importantly, several recent advances have been made in the treatment of PCNSL. The incorporation of targeted therapy and immune therapy remain promising strategies. Several agents, successfully used in treatment of systemic lymphomas, have shown activity in PCNSL, frequently leading to durable responses in the relapsed/refractory patients. Many ongoing studies will likely lead to a better understanding of the roles of these treatments, especially as the first line and potentially also as maintenance. In addition, the use of molecular profiling to predict disease response to targeted agents and understand relapse patterns will become increasingly important. Clinical trials in PCNSL are critical yet frequently challenging to conduct given the rarity of the condition and lack of suitable subjects. Therefore, multi-institutional and international collaboration is of utmost importance to accelerate progress in understanding the biology and design better treatments for this disease. It is critical to consider patients of all demographics in the design and study of future treatment algorithms to have the largest impact on patient care and outcomes.

Introduction

Primary CNS lymphomas account for approximately 4% of all newly diagnosed intracranial neoplasms [1, 2]. Primary central nervous system lymphomas (PCNSLs) are an aggressive form of non-Hodgkin lymphoma that develops within the brain, spinal cord, eye, or leptomeninges without evidence of systemic involvement. There is a higher incidence of PCNSL in males than females, the immunocompromised, and with increasing age in the white population, with those aged 75 years and older having the highest rates of incidence. Blacks, aged under 50 years at diagnosis, have a higher incidence when compared with whites, and it is unclear if this may be related to a higher incidence of underlying human immunodeficiency virus (HIV)-associated PCNSL [1, 3]. PCNSL can also occur in 7–15% of patients with immunocompromised secondary to post-transplant lymphoproliferative disorders (PTLD), which is associated with poor prognosis [4, 5].

Pathologically, PCNSL is an angiocentric neoplasm composed of monoclonal proliferation of lymphocytes. Most cases are diffuse large B cell lymphoma and characterized as the activated B cell-like/non-germinal center (ABC or NGC) subtype [6•, 7, 8]. The brain parenchyma is most commonly involved but leptomeningeal involvement occurs in 30% and ocular involvement may occur in 10–20% of patients [8]. More rarely, PCNSL can present without concurrent parenchymal involvement as primary leptomeningeal lymphoma (PLML) or primary ocular lymphoma (POL) [9, 10].

Signs and symptoms of disease can include mental status changes, including neuropsychiatric symptoms, elevated intracranial pressure, seizures, and focal deficits, and patients should be initially assessed with brain magnetic resonance imaging (MRI) [8]. PCNSL is chemo- and radiosensitive but remissions are usually short lasting, particularly due to limitations of access by many drugs through the blood-brain barrier (BBB) [11]. Surgery has a very limited role in treatment, typically only reserved for diagnosis [11]. The optimal drug combination and the role of radiotherapy, in particular for relapsed/refractory patients, has not yet been identified [11, 12]. Outcomes are better for younger patients with PCNSL, whereas in elderly patients, outcomes are poor with fewer than half of patients alive at 1 year [13, 14]. The median overall survival (OS) for immunocompetent adults is approximately 25 months [15].

Treatment of newly diagnosed PCNSL

Initial evaluation

Following a brain MRI suggestive of PCNSL, tissue biopsy is the preferred diagnostic approach, although cerebrospinal fluid (CSF) sampling to aid in diagnostic confirmation is also recommended. Ideally, steroids are withheld prior to diagnosis if possible, given the known cytolytic effect of steroids on lymphoma cells and the potential for subsequent false-negative biopsy results [16, 17]. The subsequent evaluation of PCNSL following a positive diagnosis is to confirm extent of disease as clinically indicated prior to therapy initiation, including a full ophthalmologic exam, spine MRI, systemic computed tomography (CT) or positron emission tomography (PET)/CT imaging, bone marrow biopsy, testicular ultrasound for men over age 60, and baseline labs. Steroids may also be initiated as needed for symptom management [17].

Induction therapy

The treatment of PCNSL is based on age and performance status, utilizing an individualized treatment that aims at prolonging survival while minimizing toxicity. High-dose methotrexate (HD-MTX)-based regimens are the currently accepted standard first-line therapy unless a contraindication to MTX exists; however, the optimal combination of therapies with MTX is unknown. A recent meta-analysis of clinical trials focused on first-line induction and consolidation

treatment aimed to determine the best proposed regimen [18]. There were improved complete response rates (CRRs) noted with the use of multi-drug regimens with a HD-MTX backbone compared to therapy with HD-MTX alone (pooled CRRs of 30%, 38%, 49%, and 44% for HD-MTX alone or with two, three, or four drug combination regimens, respectively) [18]. Among drug combinations, the highest CRRs were achieved through use of HD-MTX with procarbazine and vincristine (MPV) (pooled CRRs of 63% and 58% with and without rituximab, respectively) and HD-MTX with rituximab and temozolomide (MTR) (pooled CRR of 60%) [18]. While the magnitude of the effect of rituximab inclusion in regimens has remained controversial, it remains commonplace to include rituximab in induction therapy. Both of these regimens may therefore represent the most reasonable options to consider; however, of note, this analysis excluded studies with a focus on treatment in elderly patients [18]. Separately, a meta-analysis of therapy in elderly patients aged 60 and over revealed most patients (73%) still received HD-MTX-based therapy resulting in improved survival, and many received whole-brain radiotherapy [19]. HD-MTX including in combination with oral chemotherapy yielded no difference in survival compared to more aggressive HD-MTX-based therapies, indicating elderly patients may not derive added benefit from a more aggressive approach [19]. Importantly, elderly patients have been shown to tolerate MTX monotherapy well with dosing adjusted for creatinine clearance [20]. MTX doses of at least 3 g/m^2 are recommended for adequate CSF penetration, and infusion rate also plays an important role [21]. In addition, while WBRT improved outcome in the elderly, it was associated with increased risk for neurological side effects and its use for elderly patients in up front therapy is currently discouraged unless patients have contraindications to all other therapies [19]. The availability for enrollment to clinical trials therefore remains a critical option for elderly patients with limitations for standard regimens.

Role of consolidation

Given the high rate of relapse of PCNSL, consolidation therapy, initiated after complete response (CR) or complete response unconfirmed (CRu) following induction therapy, is recommended to maximize elimination of microscopic residual disease translating to improved overall response rates (ORR) to therapy [15, 22]. Consolidation regimens include high-dose chemotherapy with stem cell rescue (HDC-ASCT), high-dose cytarabine ± etoposide, or reduced dose whole brain radiation therapy (rdWBRT) [17]. If residual disease is present post induction therapy, whole brain radiation therapy, high-dose cytarabine ± etoposide, or best supportive care are all potential options [17]. Studies directly comparing consolidation regimens are limited. Results from the CALGB 51101 randomized phase 2 study evaluating the role of myeloablative versus non-myeloablative consolidative chemotherapy for newly diagnosed PCNSL after completing induction MTR plus once cycle of cytarabine (MTRA) were recently presented. Patients were stratified on age and performance status and randomized to receive either consolidation with thiotepa and carmustine followed by ASCT versus one cycle of cytarabine and etoposide [23]. Patients randomized to the myeloablative arm had an improved progression-free survival (PFS) compared to the non-myeloablative consolidation; however, there were more progressions or deaths prior to consolidation start in the non-myeloablative arm

[23]. In addition, a recent retrospective analysis of 1620 patients with PCNSL in the comprehensive national cancer database examined outcomes of consolidation with HDC-ASCT versus WBRT using propensity score matching and identified an improved OS with ASCT compared with WBRT (adjusted 3-year OS 82% versus 67%, respectively) [24]. As older patients were less likely to have received ASCT, this study does not fully address the role of factors influencing treatment selection, and the optimal treatment in the elderly remains in question. While the high rate of neurotoxicity with WBRT may outweigh the benefit of use, especially in the treatment of older adults, the use of rdWBRT as a consolidation regimen is under ongoing investigation. Early phase and retrospective studies indicate decreased neurotoxicity with similar overall patient survival compared to high-dose WBRT, including in elderly patients [25, 26]. Long-term neurologic evaluation is limited however, and more recent studies suggest there may be delayed neurotoxicity concerns [27]. Additional prospective studies are ongoing to further define the role of radiation in this setting (clinicaltrials.gov NCT01399372).

Among patients who undergo ASCT, several high-dose chemotherapy regimens have been studied. A recent meta-analysis across studies of ASCT for PCNSL found that the conditioning regimens of thiotepa, busulfan, and cyclophosphamide (TBC) or carmustine and thiotepa (BCNU/TT) have been associated with the highest response rates and lowest relapse rates after ASCT (90% and 91% response, and 10% and 21% relapse, respectively) [28]. TBC chemotherapy was associated with higher transplant-related mortality, however (3% versus 0%, respectively) [28].

Current treatment of relapsed/refractory disease

While response rates to HD-MTX-based induction therapy are high at 70–90%, most patients do not sustain long-term remission, and relapses occur most often within the first 2 years from initial response [29, 30]. Median OS remains between 40 and 70 months [29], and median time to death following relapse in patients who do not receive any salvage therapy is poor at 2 months [31]. Treatment of relapsed or refractory disease is in part guided by response to primary therapy, location of recurrence, patient age, and fitness; however, most studies guiding selection of regimens are retrospective analyses. In general, patients with appropriate performance status will either be considered for a rechallenge with HD-MTX or an alternative aggressive systemic therapy approach, followed by consideration of consolidation with high-dose chemotherapy and autologous stem cell transplantation. Patients not suitable for HD-MTX or alternative aggressive therapy will be considered for lower intensity or palliative therapies. National Comprehensive Cancer Network (NCCN) guidelines recommend consideration for rechallenge with high-dose MTX in the scenario of a previous long duration of response to MTX, defined by at least 12 months, and selection of alternative regimens in case with previous short duration or no response. Retrospective studies profiling rechallenge with salvage MTX-based regimens in patients with an initial MTX response characterize an overall response rate of 85–91%, with a median OS of 41–61.9 months following relapse [29, 32]. Of note, some patients subsequently received

additional consolidation treatments likely contributing to duration of disease control [29].

Patients who are deemed to be ineligible for rechallenge with MTX are typically considered for treatment with temozolomide alone or in combination with rituximab, pemetrexed, or high-dose cytarabine-based regimens or monotherapy, and subsequent high-dose chemotherapy with autologous stem cell transplant in eligible patients [33, 31, 34–45]. WBRT offers an alternative treatment strategy for patients with serially relapsed disease or who are not chemotherapy eligible, and while discouraged for use in first-line therapy, WBRT may still have a role in the relapsed/refractory setting. PCNSL is radiosensitive and WBRT for salvage treatment is associated with overall response rates of 74–79%; however, duration of response is short lived with most recurrences presenting within 1 year. Consideration must still be made given the association of WBRT with neurotoxicity, especially in the elderly [46–48]. Given these limited options for salvage therapy in PCNSL, the development of novel therapies based on molecular insights from tumor profiling has led to additional targeted options either recently approved or currently under investigation for relapsed/refractory disease.

Role of molecular profiling in novel therapy development

Molecular profiling performed from diagnostic tissue biopsies has played a role in characterizing the biology of PCNSL and directing the approach to novel therapy selection. Treatment-naïve PCNSL is most often classified as activated B cell-like/non-germinal center (ABC or NGC) type B cell lymphoma, which is associated with a poorer prognosis in systemic diffuse large B cell lymphoma (DLBCL) [49, 50]. Signaling pathways found in NGC DLBCL including those with secondary CNS involvement are also activated in PCNSL, including the B cell receptor (BCR) and toll-like receptor (TLR) pathways through activating mutations in MYD88 (most commonly at L265P) and CD79B (most commonly at Y196) and leading to downstream activation of NF-κB, commonly via Bruton's tyrosine kinase (BTK) signaling [51, 6, 52]. These mutations are most often mutually exclusive with other systemic DLBCL signatures including translocations of BCL2, BCL6, and cMYC or with Epstein-Barr virus (EBV) infection, which are more typical of the germinal center (GC) type of B cell lymphoma [53], and moreover, CD79B alterations may be exclusively found in the NGC subtype [6•]. Notably, among all systemic sites of NGC DLBCL, MYD88 and CD79B mutations are particularly prevalent in the historically viewed "immune privileged" B cell lymphoma sites including the CNS and testes, as compared to those arising in the lymph nodes, gastrointestinal tract, or other extranodal sites [53]. Epigenetic profiling of PCNSL has also identified an overlapping signature to some systemic DLBCL; however, overall, there is an increased predominance of methylated cytosine-phosphate-guanine sites in PCNSL compared to systemic DLBCL [54] (Table 2).

Within all PCNSL, other commonly identified alterations include additional mediators or targets of BCR-NF-κB signaling (IRF4/MUM1 and CARD11), chromatin and transcriptional regulators (MYC, PRDM1, and KMT2D), or cell cycle/apoptosis regulators (TP53, CCND3, BTG2, PIM1, CDKN2a, and ATM) [6•]. Similar to CD79B, alterations of IRF4/MUM1, MYC, and CARD11 are

characteristic of the NGC subtype, whereas GC PCNSL is more likely to display alterations in TP53 and PAX5 [6•]. In addition, aberrant somatic hypermutation (aSHM), often seen in DLBCL, has also been identified in PCNSL and frequently affects several of these known proto-oncogenes, including PIM1, MYC, RHOH/TTF, and PAX5 [55]. Moreover, somatic hypermutation has been shown to increase self- and polyreactivity for proteins expressed in the CNS, thereby facilitating unique B cell receptor signaling within PCNSL that may allow for improved tumor survival in the CNS [56]. The characterization of the divergent molecular signatures within PCNSL and compared to systemic DLBCL including secondary CNS involvement continues to inform therapeutic target selection for further development of PCNSL treatment regimens. Several strategies have been recently employed for use in salvage therapy, and the development of further investigational regimens remains ongoing.

Novel therapies in PCNSL

Targeted therapy with recent NCCN indication

Ibrutinib

Given the role that BCR signaling has been shown to play in PCNSL, the investigation of inhibitors to key pathway drivers has been of great interest in PCNSL therapeutic development. Ibrutinib, an inhibitor to BTK, was studied in two recent prospective clinical trials as monotherapy for relapsed/refractory disease. A dose-escalation study of ibrutinib 560 to 840 mg revealed a CR in 39% (5/13) and partial response (PR) in 39% (5/13) of patients, with a median PFS of 4.6 months [57••]. A larger study in 52 patients utilizing ibrutinib 560 mg daily for relapsed/refractory PCNSL and primary vitreoretinal lymphoma (PVRL) found a CR rate of 19% (10/52) and a PR of 33% (17/52), with a median PFS of 4.8 months [58••]. Ibrutinib was generally well tolerated with cytopenias representing the most common adverse event; ibrutinib was detectable in the CSF following treatment [58••, 57••]. These trials indicated use of ibrutinib is a reasonable strategy and given the high response rates, ibrutinib monotherapy is included in NCCN for treatment of relapsed/refractory PCNSL; however, duration of response was short lived in this setting.

Ibrutinib in combination with other therapies has also been studied, however remains investigational. The combination of ibrutinib with multi-agent chemotherapy not including a HD-MTX-based regimen resulted in a significant number of patients with severe CNS or pulmonary *Aspergillus* infection [59]. In a separate phase 1b study utilizing ibrutinib in combination with HD-MTX and rituximab for relapsed/refractory patients, no dose-limiting toxicities were observed; however, cytopenias were common. The ORR was 89% (8/9), and the median PFS for the PCNSL cohort had not yet been reached at the time of study publication; however, the survival may be impacted by several patients subsequently undergoing HDC-ASCT

following remission [60]. Ibrutinib in combination with other regimens, including targeted therapy, immune therapy, and other chemotherapy, is actively being studied in several clinical trials currently underway.

Lenalidomide and pomalidomide

The immunomodulatory drugs (IMiDs) lenalidomide and pomalidomide have been studied in relapsed/refractory PCNSL either as monotherapy or in combination with rituximab. IMiDs have been shown to exert direct antineoplastic effects via several mechanisms including downregulation of IRF4 leading to decreased NF-κB signaling, as well as indirect effects of immune modulation on the tumor microenvironment [61]. Moreover, lenalidomide has been shown to have higher response rates in the ABC subtype of DLBCL [61]. A phase 1 investigation of lenalidomide ± addition of rituximab at progression in six patients with relapsed PCNSL revealed one CR with a PFS greater than 48 months, and otherwise mostly partial responses, with a range of PFS values between 1.5 and 21 months [62]. The maximum tolerated dose was deemed to be 15 mg daily for 21 days out of 28; however, this was determined based off the entire cohort which also included patients with secondary CNSL (SCNSL) [62]. A separate later phase II study of lenalidomide (20 mg/day, days 1–21) in combination with rituximab in patients with relapsed/refractory PCNSL or PVRL evaluated 45 patients for response assessment (34 PCNSL and 11 PVRL) and revealed a CR rate of 35% (12/34) and PR of 29% (10/34) in the PCNSL cohort. Six patients with PVRL achieved an ocular CR [63]. Patients who responded to treatment continued with maintenance lenalidomide at 10 mg/day, days 1–21, and the median PFS for the PCNSL and PVRL cohorts were 3.9 and 9.2 months, respectively. Hematologic toxicity was the most commonly reported adverse event [63].

Pomalidomide, a third-generation IMiD with preclinical activity in CNSL, has also been studied in patients with PCNSL. A phase 1 study of pomalidomide and dexamethasone in relapsed/refractory PCNSL or PVRL evaluated 25 patients for response assessment (23 PCNSL, 2 PVRL) [64]. The ORR was 48%, including 6 CR, 2 CRu, and 4 PRs, with a median PFS of 5.3 months (9 months in responders). The maximum tolerated dose of pomalidomide was 5 mg/day for 21 days out of 28 [64]. Based on these data, lenalidomide and pomalidomide were incorporated into NCCN guidelines for relapsed/refractory disease, and further multi-agent regimens incorporating IMiDs in PCNSL remain under ongoing investigation.

In patients with transplant ineligible relapsed/refractory DLBCL, ibrutinib in combination with lenalidomide and rituximab has been shown to have activity particularly in the NGC subtype in a phase 1b dose-escalation study using ibrutinib 560 mg daily and lenalidomide dosing between 10 and 25 mg [65]. The ORR for patients with NGC DLBCL (n = 17) was 65%, including 41% CR, and among responders, the median duration of response was 15.9 months [65]. While patients with secondary CNS disease who have a known poor prognosis [66] were excluded from this study, the

activity of these known CNS penetrant drugs in combination in particular in the NGC lymphoma subtype is promising in support of using similar combination treatments in PCNSL.

Investigational therapies

Second-generation BTK inhibitors

While the continued investigation of ibrutinib in PCNSL remains ongoing, there is also a recent phase I/II report of the second-generation BTK inhibitor tirabrutinib, a highly selective and irreversible oral BTK inhibitor in relapsed/refractory PCNSL. While there were no dose-limiting toxicities in this study, nearly half of patients had a grade three or higher adverse event mostly involving cytopenias. Six patients had serious adverse drug reactions which included bronchopulmonary aspergillosis in one patient and interstitial lung disease and pneumocystis pneumonia in another patient. The overall response rate was 64%; however, durability was poor with median PFS of 2.9 months [67]. A clinical trial is underway to study the use of an alternative second-generation BTK inhibitor, acalabrutinib, in combination with durvalumab in PCNSL (clinicaltrials.gov NCT04462328). Thus, the role of these agents remains promising, but data are still emerging in order to better characterize the role of subsequent generation BTK inhibitors in PCNSL.

PI3K/mTOR pathway

Preclinical data has shown that PCNSL utilizes the PI3K/AKT/mTOR and RAS/MAPK pathways to regulate metabolism, with increased pathway signaling noted in particular in MTX-resistant PCNSL cell lines [68]. Targeting the PI3K/mTOR pathway remains under investigation in PCNSL. A phase II study of the mTOR inhibitor temsirolimus for relapsed/refractory PCNSL revealed an overall response rate of 54%; however, duration of response was short with median PFS of 2.1 months and several patients had significant grade 3 toxicities for cytopenias and infection [69]. Buparlisib, a pan-PI3K inhibitor, has also been studied in a phase II trial with relapsed/refractory PCNSL and SCNSL. This trial closed early due to limited clinical response, which may have been impacted by CNS drug concentrations below a meaningful IC_{50} concentration [70]. Copanlisib is currently under investigation in combination with ibrutinib for patients with relapsed/refractory disease (clinicaltrials.gov NCT03581942).

Immune checkpoint blockade

The role of immune checkpoint blockade in PCNSL remains unclear. Studies profiling the expression of immune response biomarkers have indicated more than half (54.8%) of PCNSL tumors express either high PD-L1 or high tumor mutation burden (TMB), and most of the remaining tumors expressed intermediate TMB, thus indicating the potential for PCNSL patients to respond to immune checkpoint inhibitors [71]. PD-L1 and PD-L2 in PCNSL are also expressed in peritumoral or intratumoral macrophages in most patients [72]. Clinically, use of immune therapy has been isolated to case reports. One report of a 36-year-old male who became ineligible for further MTX-based therapy due

to clinical deterioration notably tolerated use of nivolumab and subsequently had a documented prolonged remission [73]. Separately, a case series of four relapsed/refractory PCNSL patients treated with nivolumab revealed all patients had clinical and radiographic response to treatment and some patients have demonstrated durability of response in early follow-up analysis [74]. These early isolated studies are promising and require further investigation. Multiple studies are underway testing use of immune therapy monotherapy for relapsed disease, or alternatively in combination with other targeted therapy, or for use as consolidation in older patients.

Adaptive T cell therapy

The use of chimeric antigen receptor (CAR) T cell therapy has been recently approved for relapsed/refractory DLBCL based off the ZUMA-1 and JULIET clinical trials; however, these earlier studies excluded patients with secondary CNS disease out of concern that CNS disease may increase the risk or severity of treatment-related neurotoxicity. More recently, there is now accumulating evidence that use of CD19-directed CAR-T therapy in patients with CNS disease may be a feasible treatment strategy. Three recent studies profile the use of tisagenlecleucel or axicabtagene ciloleucel CAR-T cell therapies, and additionally one recent case report profiles the use of lisocabtagene maraleucel (JCAR017) CAR-T cell therapy in patients with active secondary CNS lymphoma. All studies reported patients with CNS disease response, indicating CAR-T cells were able to traffic to the CNS [75–78], and moreover, anti-CD19 CAR-T cells have been identified in the cerebrospinal fluid, supporting their ability to cross the BBB [78–80]. Importantly, there was no apparent increase in expected cytokine release syndrome (CRS) or neurotoxicity [75–78], and active systemic disease was not required for CAR-T cell expansion and disease response [75]. A separate case report profiling the use of dual CD19 and CD70-directed CAR-T therapy in a patient with relapsed PCNSL indicated the patient experienced no CRS or neurotoxicity and remained in remission through the 17-month follow-up at the time of publication [81]. Given these findings, use of CAR-T cell therapy in patients with relapsed/refractory PCNSL remains an attractive strategy and several clinical trials are currently enrolling for this indication (clinicaltrials.gov NCT04443829, NCT04608487, NCT04464200). Additionally, tabelecleucel T cell immunotherapy is under investigation for Epstein-Barr virus (EBV)-associated diseases including EBV+ post-transplant lymphoproliferative disease in the CNS (clinicaltrials.gov NCT04554914). Table 1 summarizes novel and investigational therapies in PCNSL.

Future directions for targeted therapy

Additional agents are under investigation with no clinical data yet published. A current phase 2 study will assess the use of the CDK4/6 inhibitor abemaciclib in recurrent brain tumors, including a PCNSL cohort (clinicaltrials.gov NCT03220646). The proteasome inhibitor bortezomib as monotherapy or in combination with chemotherapy is also under study including in cohorts of patients with PCNSL (clinicaltrials.gov NCT00598169, NCT00004002, NCT00544284). The BCL2 inhibitor venetoclax in combination with obinutuzumab is also in study (NCT04073147).

Table 1. Comparison of primary CNS lymphoma and secondary CNS lymphoma

	Primary CNS lymphoma	Secondary CNS lymphoma
Definition	Origin in the central nervous system and confined to areas including the brain, spine, and CSF	CNS disease presents either concurrent to systematic lymphoma or as secondary progression of systemic lymphoma
Pathology	Primarily DLBCL (90%) but also rarely includes Burkitt, low-grade, or T cell lymphoma [2]	DLBCL, Burkitt lymphoma
Risk factors	Immunodeficiency and older age [2]	Advanced stage (stage III or IV), extralymphatic sites of involvement, age > 60 [52]
Clinical presentation	Focal neurologic deficits, personality changes, symptoms of increased intracranial pressure, seizures [2]	Headaches, cranial nerve palsies, change in neurologic status, seizures, coma [52]
Molecular subtype	Activated B cell origin phenotype (80–95%) or germinal center B cell phenotype (5–13%) [6•]	Activated B cell origin phenotype (47%) or germinal center B cell phenotype (53%) [6•]
Outcome	Median overall survival 24 months; 5-year survival 30–40% [15]	Median overall survival 2.2 months [66]

Role for maintenance therapy?

In younger fit patients who typically follow a more aggressive strategy for induction and consolidation therapy, there are currently no standard guidelines for maintenance therapy [82]. However, several therapies have been investigated for use as maintenance therapy, and this may be a particularly attractive strategy for use in the elderly who are unable to tolerate more aggressive up-front regimens (Table 2). Currently, the optimal treatment strategy in the elderly remains poorly defined given the concern of neurotoxicity with WBRT, as well as the significant toxicity in autologous stem cell transplant or high-dose chemotherapy consolidation regimens. A retrospective analysis on the use of maintenance temozolomide monotherapy in elderly patients found this regimen to display activity and be generally well tolerated, allowing for an alternative strategy when more aggressive regimens are contraindicated [83], and prospectively, temozolomide maintenance in patients older than 65 years of age following HD-MTX-based induction demonstrated a 2-year OS of 60% [84]. Procarbazine maintenance has also been studied in the elderly (age > 65) population, with 2-year OS of 47% [85]. Moreover, maintenance therapy with HD-MTX has been a routinely used strategy which may improve the prognosis for PCNSL in the elderly patient [86, 20].

In addition to chemotherapy regimens and given the promising results in relapsed/refractory PCNSL, the use of ibrutinib or lenalidomide as an alternative maintenance strategy remains under ongoing study across all ages. A recent phase I investigation of lenalidomide maintenance after response to salvage therapy in relapsed/refractory PCNSL identified a potentiated duration of response leading to a delay in need for subsequent WBRT in patients [62]. A

Table 2. Novel and investigational therapies for PCNSL

Author, year	Regimen	Number of PCNSL patients	Median age (years)	Response rate	mPFS, mOS (months)	Most common grade 3/4 adverse events
Grommes, 2017 [57••]	Ibrutinib monotherapy. Dose escalation 560 mg, 700 mg, 840 mg oral daily	13 (relapsed/refractory PCNSL)	69	PR: 5/13 (39%) CR: 5/13 (39%)	mPFS 4.6 mo mOS 15 mo	Lymphopenia, neutropenia, hyperglycemia
Soussain, 2019 [58••]	Ibrutinib monotherapy. 560 mg oral daily	52 (relapsed/refractory PVRL and PCNSL)	69	PR: 17/52 (33%) CR: 10/52 (19%)	mPFS 4.8 mo mOS 19.2 mo	Neutropenia, ALT elevation, GGT elevation
Lionakis, 2017 [59]	Ibrutinib followed by ibrutinib/DA-TEDDi-R	18 (5 treatment-naïve PCNSL, 13 relapsed/ refractory PCNSL)	66	PR: 1/14 (7%) CR/CRu: 12/14 (86%)* *2 patients died during ibrutinib window; *2 patients with deaths prior to cycle 2 restaging unrelated to treatment	mPFS 15.3 mo mOS not reached	Neutropenia, febrile neutropenia, thrombocytopenia, pulmonary infection *Grade 5: pulmonary/ CNS aspergillosis (2 patients), febrile neutropenia (1 patient), stroke (1 patient), ventricular arrhythmia (1 patient)
Grommes, 2019 [60]	Ibrutinib/HD-MTX/ rituximab	9 (relapsed/refractory PCNSL)	62	PR: 2/9 (22%) CR: 6/9 (67%)	mPFS not reached	Lymphopenia, neutropenia, anemia, AST elevation, lung infection
Rubenstein, 2018 [62]	Lenalidomide monotherapy 10–20 mg/day, followed by lenalidomide/ rituximab with disease progression	6 (relapsed/refractory PCNSL)	66	PR: 5/6 (83%) CR: 1/6 (17%)	PFS range (1–48+ mo)	Infection (1 patient), neutropenia (1 patient)
Ghesquieres, 2019 [63]	Lenalidomide (20 mg/day D1–21 every 28)/rituximab induction, followed by lenalidomide maintenance	45 (relapsed/refractory PCNSL (34) and PVRL (11))	69	PCNSL: CR: 12/34 (35%) PR: 10/34 (29%) PVRL: CR: 6/11 (55%) with ocular CR	mPFS 7.8 mo (3.9 mo-PCNSL; 9.2 mo-PVRL) mOS 17.7 mo	Neutropenia, pneumonitis, asthenia, paresthesia, rash

Table 2. (Continued)

Author, year	Regimen	Number of PCNSL patients	Median age (years)	Response rate	mPFS, mOS (months)	Most common grade 3/4 adverse events
	(10 mg/day D1–21 every 28)					
Tun, 2018 [64]	Pomalidomide (3 mg, 5 mg, or 7 mg D1–21 every 28)/ dexamethasone 40 mg weekly for 8 weeks	25 (relapsed/refractory PCNSL (23), PVRL (2))	Not reported	PR: 4/25 (16%) CR/CRu: 8/25 (32%)	mPFS 5.3mo mOS not reported	Neutropenia, anemia, thrombocytopenia, lung infection
Narita, 2021 [67]	Tirabrutinib 320 mg or 480 mg oral daily	44 (relapsed/refractory PCNSL)	60	PR: 13/44 (29.5%) CR/CRu: 15/44 (34.1%)	mPFS 2.9 mo mOS not reached	Neutropenia, leukopenia, erythema multiforme
Korfel, 2016 [69]	Temsirolimus 25 mg or 75 mg intravenously weekly	37 (relapsed/refractory PCNSL)	70	PR: 12/37 (32.4%) CR/CRu: 8/37 (21.6%)	mPFS 2.1 mo mOS 3.7 mo	Hyperglycemia, thrombocytopenia, infection, anemia, rash
Grommes, 2016 [70]	Buparlisib 100 mg oral daily	2 (relapsed/refractory PCNSL)	Not reported	PR*: 1/4 (not reported whether this occurred in the PCNSL patients, $n = 2$, or SCNSL patients, $n = 2$) CR: 0/4	mPFS 39 days mOS 196 days *Trial closed prematurely due to limited response	Lymphopenia, neutropenia
Nayak, 2017 [74]	Nivolumab 3 mg/kg intravenously every 2 weeks	4 (relapsed/refractory PCNSL)	64	PR: 1/4 (25%) CR: 3/4 (75%)	PFS range (14–17+ mo)	Worsened renal insufficiency (1 patient)
El-Tawab, 2020 [73]	Nivolumab 3 mg/kg intravenously every 2 weeks	1 (relapsed/refractory PCNSL)	36	CR: 1/1	mPFS not reached at time of publication	No toxicity documented
Tu, 2019 [81]	CD19- and CD70-CAR T cells	1 (relapsed/refractory PCNSL)	67	CR: 1/1	mPFS not reached (f/u of 17 mo)	No CRS or CRES

DA-TEDDi-R, dose-adjusted temozolomide, etoposide, doxil, dexamethasone, ibrutinib, rituximab + intrathecal cytarabine; *CRES*, CAR-T-related encephalopathy syndrome

separate study revealed low-dose lenalidomide (5–10 mg/day) maintenance following induction in older patients aged 70 and over with PCNSL was well tolerated [87]. Thus, the optimal use of maintenance therapies across PCNSL populations remains an area of ongoing debate and active study.

Challenges and special considerations in PCNSL treatment

There remain several ongoing challenges within the management of PCNSL. Within this uncommon diagnosis are the rare subsets of PCNSL patients with PLML or POL, both of which can represent a diagnostic challenge. The clinical presentation of PLML can include multi-focal symptoms at onset that refer to multiple neuraxial levels and some patients may require a meningeal biopsy for confirmation [10]. Moreover, there is a higher representation of T cell lymphoma within PLML than PCNSL as a whole and there are no established standard treatment paradigms for this disease with survival outcomes quite variable with no clear outcome predictors [10]. POL is uniquely characterized by an increased predominance of mucosa-associated lymphoid tissue (MALT) lymphoma subtype, followed by DLBCL and follicular lymphoma [88]. Importantly within POL, this disease may secondarily progress to involve the brain parenchyma in most patients, and diagnosis may be missed while the lymphoma is confined to the ocular space [9]. Ocular symptoms, which typically include unilateral floaters or blurred vision, scotoma, or less commonly decreased visual acuity, may precede the diagnosis of PCNSL by 1 month to 10 years [9]. POL is commonly treated with radiation; however, it also responds to systemic chemotherapy used in PCNSL, and frequently, this approach is favored over ocular radiation. Moreover, intraocular chemotherapy can also be used to often induce an initial or second remission [9, 88]. Notably, PCNSL may secondarily progress to have intraocular involvement, which may not be associated with any ocular symptoms [9]. Thus, the continued evaluation for ocular spread remains an important concern in the treatment of PCNSL, and the limitations in recognition and treatment of the rare subsets of PCNSL represent an ongoing challenge for patient care.

The treatment of PCNSL is restricted by several factors. The BBB governs penetration of several chemotherapy regimens into the CNS that have been used in systemic DLBCL. Several studies aimed at improving the permeability of the BBB to increase effective chemotherapy delivery have been tried, but this strategy is currently limited to clinical trials [89]. The use of intrathecal chemotherapy may have a role, but also requires further investigation, and both strategies require ongoing assessment for potentially increased neurotoxicity. Moreover, there are challenges with response assessment, as patients with residual enhancement following therapy who would otherwise meet criteria for a complete response are often classified as a "complete response unconfirmed" (CRu) [90]. The residual enhancement may represent biopsy-related change or focal hemorrhage [90]. Given these patients are treated effectively as though they are in CR, they will require serial imaging for stability assessment in their ongoing evaluation.

In addition, as patients live longer with PCNSL, there remains a concern for delayed neurotoxicity which can significantly impact quality of life. A recent longitudinal study of patients who remained progression free of disease at 5 years following induction chemotherapy and either rdWBRT or HDC-ASCT evaluated patient cognition through combined neuropsychiatric measures and brain imaging

[27]. While both groups had initial improvement of cognitive function through year 3 post treatment, there was a subsequent decline in neurocognitive function with increasing structural brain abnormalities at later time points [27]. Given the impact on patient morbidity, many ongoing trials now incorporate standardized metrics of cognition assessment into the protocols.

Moreover, it will be important to address any healthcare inequalities in both the access to standard therapies and to enrollment in clinical trials in order to more broadly translate efficacy results for novel therapies across diverse populations in the ongoing studies for improved treatment of PCNSL. Historically, HIV-associated PCNSL had been excluded from PCNSL clinical trials. HIV-PCNSL is typically Epstein-Barr virus (EBV) associated, and prior to the use of combined antiretroviral therapy (cART) for HIV, patients were ineligible for high-dose chemotherapy due to profound immunosuppression and were often treated with WBRT, with survival times of a few months [91]. More recently, use of cART has allowed patients with HIV-PCNSL to be treated with HD-MTX-based regimens, which resulted in the long-term survival of a cohort of patients in retrospective analysis [92]. Subsequent consideration for HDC-ASCT may be feasible as well [93]. Moreover, Blacks and Hispanics now comprise the majority of HIV-positive non-Hodgkin lymphoma patients in the USA [94], and it will be important to continue to consider this population in ongoing clinical trials with novel therapies.

Summary

PCNSL represents a rare primary CNS malignancy with evolving treatment algorithms in particular in relapsed/refractory disease. When available, our practice is to enroll patients in clinical trials both in the newly diagnosed and the relapsed/refractory setting. Our preferred first-line regimen is MTR as standard of care given patient tolerability and response rates. For young and fit patients, we typically consolidate with ASCT in CR1 using carmustine and thiotepa myeloablative conditioning regimen. For transplant-ineligible patients including the elderly, we opt to use cytarabine alone or combined with etoposide for non-myeloablative consolidation. We avoid consolidation with WBRT due to concerns regarding neurocognitive decline and consider rdWBRT if radiation therapy is indicated. Our practice for the preferred second-line therapy is largely dependent of the previously prescribed first-line therapy and the duration of such therapy. For a patient with a long duration of response to first-line HDMTX, we consider rechallenge with HDMTX (± rituximab) followed by a BTK inhibitor. For a patient with a short duration of response to first-line HDMTX, and depending on the initial consolidation regimen, we frequently consider high-dose cytarabine for fit patients and/or one of the novel agents, specifically BTK inhibitors. While not a standard of care, we have occasionally used radiosurgery for focal recurrences followed by maintenance therapy with a BTK inhibitor or an immunomodulator such as lenalidomide.

Compliance with Ethical Standards

Conflict of Interest

The authors declare no competing interests.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 2011;105(9):1414–8. https://doi.org/10.1038/bjc.2011.357.
2. Grommes C, DeAngelis LM. Primary CNS lymphoma. J Clin Oncol. 2017;35(21):2410–8. https://doi.org/10.1200/JCO.2017.72.7602.
3. Pulido JS, Vierkant RA, Olson JE, Abrey L, Schiff D, O'Neill BP. Racial differences in primary central nervous system lymphoma incidence and survival rates. Neuro-Oncology. 2009;11(3):318–22. https://doi.org/10.1215/15228517-2008-103.
4. Buell JF, Gross TG, Hanaway MJ, Trofe J, Roy-Chaudhury P, First MR, Woodle ES. Posttransplant lymphoproliferative disorder: significance of central nervous system involvement. Transplant Proc. 2005;37(2):954–5. https://doi.org/10.1016/j.transproceed.2004.12.130.
5. Cavaliere R, Petroni G, Lopes MB, Schiff D, International Primary Central Nervous System Lymphoma Collaborative G. Primary central nervous system post-transplantation lymphoproliferative disorder: an International Primary Central Nervous System Lymphoma Collaborative Group report. Cancer. 2010;116(4):863–70. https://doi.org/10.1002/cncr.24834.
6.• Bodor C, Alpar D, Marosvari D, Galik B, Rajnai H, Batai B, Nagy A, Kajtar B, Burjan A, Deak B, Schneider T, Alizadeh H, Matolcsy A, Brandner S, Storhoff J, Chen N, Liu M, Ghali N, Csala I, et al. Molecular subtypes and genomic profile of primary central nervous system lymphoma. J Neuropathol Exp Neurol. 2020;79(2):176–83. https://doi.org/10.1093/jnen/nlz125

This paper desribes comprehensive gene expression profiling of PCNSL and outlines molecular classification.

7. Gerstner ER, Batchelor TT. Primary central nervous system lymphoma. Arch Neurol. 2010;67(3):291–7. https://doi.org/10.1001/archneurol.2010.3.
8. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, Guy G, Lapierre F. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg. 2000;92(2):261–6. https://doi.org/10.3171/jns.2000.92.2.0261.
9. Hormigo A, DeAngelis LM. Primary ocular lymphoma: clinical features, diagnosis, and treatment. Clin Lymphoma. 2003;4(1):22–9. https://doi.org/10.3816/clm.2003.n.010.
10. Taylor JW, Flanagan EP, O'Neill BP, Siegal T, Omuro A, Deangelis L, Baehring J, Nishikawa R, Pinto F, Chamberlain M, Hoang-Xuan K, Gonzalez-Aguilar A, Batchelor T, Blay JY, Korfel A, Betensky RA, Lopes MB, Schiff D. Primary leptomeningeal lymphoma: International Primary CNS Lymphoma Collaborative Group report. Neurology. 2013;81(19):1690–6. https://doi.org/10.1212/01.wnl.0000435302.02895.f3.
11. Citterio G, Reni M, Gatta G, Ferreri AJM. Primary central nervous system lymphoma. Crit Rev Oncol Hematol. 2017;113:97–110. https://doi.org/10.1016/j.critrevonc.2017.03.019.
12. Holdhoff M, Mrugala MM, Grommes C, Kaley TJ, Swinnen LJ, Perez-Heydrich C, Nayak L. Challenges in the treatment of newly diagnosed and recurrent primary central nervous system lymphoma. J Natl Compr Cancer Netw. 2020;18(11):1571–8. https://doi.org/10.6004/jnccn.2020.7667.
13. Lukas RV, Stupp R, Gondi V, Raizer JJ. Primary central nervous system lymphoma—part 1: epidemiology, diagnosis, staging, and prognosis. Oncology (Williston Park). 2018;32(1):17–22.
14. Norden AD, Drappatz J, Wen PY, Claus EB. Survival among patients with primary central nervous system lymphoma, 1973-2004. J Neuro-Oncol. 2011;101(3):487–93. https://doi.org/10.1007/s11060-010-0269-7.
15. Houillier C, Soussain C, Ghesquieres H, Soubeyran P, Chinot O, Taillandier L, Lamy T, Choquet S, Ahle G, Damaj G, Agape P, Molucon-Chabrot C, Amiel A, Delwail V, Fabbro M, Jardin F, Chauchet A, Moles-Moreau MP, Morschhauser F, et al. Management and outcome of primary CNS lymphoma in the modern era: an LOC network study. Neurology. 2020;94(10):e1027–39. https://doi.org/10.1212/WNL.0000000000008900.
16. Binnahil M, Au K, Lu JQ, Wheatley BM, Sankar T. The influence of corticosteroids on diagnostic accuracy of biopsy for primary central nervous system lymphoma. Can J Neurol Sci. 2016;43(5):721–5. https://doi.org/10.1017/cjn.2016.255.
17. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 3.2020). https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed February 03.
18. Yu J, Du H, Ye X, Zhang L, Xiao H. High-dose methotrexate-based regimens and post-remission consolidation for treatment of newly diagnosed primary CNS lymphoma: meta-analysis of clinical trials. Sci Rep. 2021;11(1):2125. https://doi.org/10.1038/s41598-020-80724-0.
19. Kasenda B, Ferreri AJ, Marturano E, Forst D, Bromberg J, Ghesquieres H, Ferlay C, Blay JY, Hoang-Xuan K, Pulczynski EJ, Fossa A, Okoshi Y, Chiba S, Fritsch K, Omuro A, O'Neill BP, Bairey O, Schandelmaier S, Gloy

V, et al. First-line treatment and outcome of elderly patients with primary central nervous system lymphoma (PCNSL)—a systematic review and individual patient data meta-analysis. Ann Oncol. 2015;26(7):1305–13. https://doi.org/10.1093/annonc/mdv076.

20. Zhu JJ, Gerstner ER, Engler DA, Mrugala MM, Nugent W, Nierenberg K, Hochberg FH, Betensky RA, Batchelor TT. High-dose methotrexate for elderly patients with primary CNS lymphoma. Neuro-Oncology. 2009;11(2):211–5. https://doi.org/10.1215/15228517-2008-067.
21. Ferreri AJ. How I treat primary CNS lymphoma. Blood. 2011;118(3):510–22. https://doi.org/10.1182/blood-2011-03-321349.
22. Liu Y, Yao Q, Zhang F. Diagnosis, prognosis and treatment of primary central nervous system lymphoma in the elderly population (review). Int J Oncol. 2021;58(3):371–87. https://doi.org/10.3892/ijo.2021.5180.
23. Batchelor T, Giri S, Ruppert AS, Bartlett NL, Hsi ED, Cheson BD, Nayak L, Leonard JP, Rubenstein JL. Myeloablative versus non-myeloablative consolidative chemotherapy for newly diagnosed primary central nervous system lymphoma: results of CALGB 51101 (Alliance). J Clin Oncol. 2021;39(15_suppl):7506-7506. https://doi.org/10.1200/JCO.2021.39.15_suppl.7506.
24. Samhouri Y, Ali MM, Jayakrishnan TT, Bakalov V, Fazal S, Khan C, Wegner RE, Lee ST, Lister J. Autologous stem cell transplantation (ASCT) versus whole brain radiation (WBRT) as a consolidation therapy in primary CNS lymphoma (PCNSL): a nationwide analysis. J Clin Oncol. 2021;39(15_suppl):2062-2062. https://doi.org/10.1200/JCO.2021.39.15_suppl.2062.
25. Lee TH, Lee JH, Chang JH, Ye SJ, Kim TM, Park CK, Kim IH, Kim BH, Wee CW. Reduced-dose whole-brain radiotherapy with tumor bed boost after upfront high-dose methotrexate for primary central nervous system lymphoma. Radiat Oncol J. 2020;38(1):35–43. https://doi.org/10.3857/roj.2020.00052.
26. Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, Grimm S, Lai RK, Reiner AS, Panageas K, Karimi S, Curry R, Shah G, Abrey LE, DeAngelis LM, Omuro A. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 2013;31(31):3971–9. https://doi.org/10.1200/JCO.2013.50.4910.
27. Correa DD, Braun E, Kryza-Lacombe M, Ho KW, Reiner AS, Panageas KS, Yahalom J, Sauter CS, Abrey LE, DeAngelis LM, Omuro A. Longitudinal cognitive assessment in patients with primary CNS lymphoma treated with induction chemotherapy followed by reduced-dose whole-brain radiotherapy or autologous stem cell transplantation. J Neuro-Oncol. 2019;144(3):553–62. https://doi.org/10.1007/s11060-019-03257-1.
28. Alnahhas I, Jawish M, Alsawas M, Zukas A, Prokop L, Murad MH, Malkin M. Autologous stem-cell transplantation for primary central nervous system lymphoma: systematic review and meta-analysis. Clin Lymphoma Myeloma Leuk. 2019;19(3):e129–41. https://doi.org/10.1016/j.clml.2018.11.018.
29. Pentsova E, Deangelis LM, Omuro A. Methotrexate re-challenge for recurrent primary central nervous system lymphoma. J Neuro-Oncol. 2014;117(1):161–5. https://doi.org/10.1007/s11060-014-1370-0.
30. Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, Hochberg F, Priet R. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol. 2003;21(6):1044–9. https://doi.org/10.1200/JCO.2003.03.036.
31. Reni M, Ferreri AJ, Villa E. Second-line treatment for primary central nervous system lymphoma. Br J Cancer. 1999;79(3-4):530–4. https://doi.org/10.1038/sj.bjc.6690083.
32. Plotkin SR, Betensky RA, Hochberg FH, Grossman SA, Lesser GJ, Nabors LB, Chon B, Batchelor TT. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. Clin Cancer Res. 2004;10(17):5643–6. https://doi.org/10.1158/1078-0432.CCR-04-0159.
33. Kasenda B, Ihorst G, Schroers R, Korfel A, Schmidt-Wolf I, Egerer G, von Baumgarten L, Roth A, Bloehdorn J, Mohle R, Binder M, Keller U, Lamprecht M, Pfreundschuh M, Valk E, Fricker H, Schorb E, Fritsch K, Finke J, Illerhaus G. 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(12):2623–9. https://doi.org/10.1038/leu.2017.170.
34. Makino K, Nakamura H, Hide T, Kuratsu J. Salvage treatment with temozolomide in refractory or relapsed primary central nervous system lymphoma and assessment of the MGMT status. J Neuro-Oncol. 2012;106(1):155–60. https://doi.org/10.1007/s11060-011-0652-z.
35. Wong ET, Tishler R, Barron L, Wu JK. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. Cancer. 2004;101(1):139–45. https://doi.org/10.1002/cncr.20339.
36. Enting RH, Demopoulos A, DeAngelis LM, Abrey LE. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. Neurology. 2004;63(5):901–3. https://doi.org/10.1212/01.wnl.0000137050.43114.42.
37. Nayak L, Abrey LE, Drappatz J, Gilbert MR, Reardon DA, Wen PY, Prados M, Deangelis LM, Omuro A, North American Brain Tumor C. Multicenter phase II study of rituximab and temozolomide in recurrent primary central nervous system lymphoma. Leuk Lymphoma. 2013;54(1):58–61. https://doi.org/10.3109/10428194.2012.698736.

38. Raizer JJ, Rademaker A, Evens AM, Rice L, Schwartz M, Chandler JP, Getch CC, Tellez C, Grimm SA. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. Cancer. 2012;118(15):3743–8. https://doi.org/10.1002/cncr.26709.
39. Sun Y, Wang Y, Han S, Xing B, Li H, Zhu Y, Zhou S, Wang X, Xu J, Tao R. Efficacy and safety of pemetrexed on recurrent primary central nervous system lymphomas in China: a prospective study. Onco Targets Ther. 2017;10:2595–600. https://doi.org/10.2147/OTT.S134684.
40. Zhang JP, Lee EQ, Nayak L, Doherty L, Kesari S, Muzikansky A, Norden AD, Chen H, Wen PY, Drappatz J. Retrospective study of pemetrexed as salvage therapy for central nervous system lymphoma. J Neuro-Oncol. 2013;115(1):71–7. https://doi.org/10.1007/s11060-013-1196-1.
41. Zhao HT, Chen J, Shi SB, Tian J, Tao RJ. Pemetrexed plus rituximab as second-line treatment for primary central nervous system lymphoma. Med Oncol. 2015;32(1):351. https://doi.org/10.1007/s12032-014-0351-7.
42. Han S, Wang M, Liu B, Yu J. Pemetrexed for primary central nervous system lymphoma in the elderly. Clin Transl Oncol. 2016;18(2):138–43. https://doi.org/10.1007/s12094-015-1345-4.
43. Chamberlain MC. High-dose cytarabine salvage therapy for recurrent primary CNS lymphoma. J Neuro-Oncol. 2016;126(3):545–50. https://doi.org/10.1007/s11060-015-1994-8.
44. Arellano-Rodrigo E, Lopez-Guillermo A, Bessell EM, Nomdedeu B, Montserrat E, Graus F. Salvage treatment with etoposide (VP-16), ifosfamide and cytarabine (Ara-C) for patients with recurrent primary central nervous system lymphoma. Eur J Haematol. 2003;70(4):219–24. https://doi.org/10.1034/j.1600-0609.2003.00045.x.
45. del Rio MS, Choquet S, Hoang-Xuan K, Glaisner S, Fourme E, Janvier M, Soussain C. Platine and cytarabine-based salvage treatment for primary central nervous system lymphoma. J Neuro-Oncol. 2011;105(2):409–14. https://doi.org/10.1007/s11060-011-0608-3.
46. Nguyen PL, Chakravarti A, Finkelstein DM, Hochberg FH, Batchelor TT, Loeffler JS. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. J Clin Oncol. 2005;23(7):1507–13. https://doi.org/10.1200/JCO.2005.01.161.
47. Hottinger AF, DeAngelis LM, Yahalom J, Abrey LE. Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. Neurology. 2007;69(11):1178–82. https://doi.org/10.1212/01.wnl.0000276986.19602.c1.
48. Laack NN, Ballman KV, Brown PB, O'Neill BP, North Central Cancer Treatment G. Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: results of North Central Cancer Treatment Group (NCCTG) 96-73-51. Int J Radiat Oncol Biol Phys. 2006;65(5):1429–39. https://doi.org/10.1016/j.ijrobp.2006.03.061.
49. Camilleri-Broet S, Criniere E, Broet P, Delwail V, Mokhtari K, Moreau A, Kujas M, Raphael M, Iraqi W, Sautes-Fridman C, Colombat P, Hoang-Xuan K, Martin A. 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(1):190–6. https://doi.org/10.1182/blood-2005-03-1024.
50. Pasqualucci L, Dalla-Favera R. The genetic landscape of diffuse large B-cell lymphoma. Semin Hematol. 2015;52(2):67–76. https://doi.org/10.1053/j.seminhematol.2015.01.005.
51. Grommes C, Nayak L, Tun HW, Batchelor TT. Introduction of novel agents in the treatment of primary CNS lymphoma. Neuro-Oncology. 2019;21(3):306–13. https://doi.org/10.1093/neuonc/noy193.
52. Steffanoni S, Doorduijin JK. Narrative review: secondary central nervous system lymphoma. Annals of Lymphoma; Vol 5 (March 2021): Annals of Lymphoma 2021. https://aol.amegroups.com/article/view/7059.
53. Kraan W, Horlings HM, van Keimpema M, Schilder-Tol EJ, Oud ME, Scheepstra C, Kluin PM, Kersten MJ, Spaargaren M, Pals ST. High prevalence of oncogenic MYD88 and CD79B mutations in diffuse large B-cell lymphomas presenting at immune-privileged sites. Blood Cancer J. 2013;3:e139. https://doi.org/10.1038/bcj.2013.28.
54. Vogt J, Wagener R, Montesinos-Rongen M, Ammerpohl O, Paulus W, Deckert M, Siebert R. Array-based profiling of the lymphoma cell DNA methylome does not unequivocally distinguish primary lymphomas of the central nervous system from non-CNS diffuse large B-cell lymphomas. Genes Chromosom Cancer. 2019;58(1):66–9. https://doi.org/10.1002/gcc.22687.
55. Montesinos-Rongen M, Van Roost D, Schaller C, Wiestler OD, Deckert M. Primary diffuse large B-cell lymphomas of the central nervous system are targeted by aberrant somatic hypermutation. Blood. 2004;103(5):1869–75. https://doi.org/10.1182/blood-2003-05-1465.
56. Montesinos-Rongen M, Terrao M, May C, Marcus K, Blumcke I, Hellmich M, Kuppers R, Brunn A, Deckert M. The process of somatic hypermutation increases polyreactivity for central nervous system antigens in primary central nervous system lymphoma. Haematologica. 2021;106(3):708–17. https://doi.org/10.3324/haematol.2019.242701.
57.•• Grommes C, Pastore A, Palaskas N, Tang SS, Campos C, Schartz D, Codega P, Nichol D, Clark O, Hsieh WY, Rohle D, Rosenblum M, Viale A, Tabar VS, Brennan CW, Gavrilovic IT, Kaley TJ, Nolan CP, Omuro A, et al. Ibrutinib unmasks critical role of bruton tyrosine kinase in primary CNS lymphoma. Cancer Discov. 2017;7(9):1018–29. https://doi.org/10.1158/2159-8290.CD-17-0613

This paper describes the role of Bruton's tyrosine kinase in PCNSL.

58.•• Soussain C, Choquet S, Blonski M, Leclercq D, Houillier C, Rezai K, Bijou F, Houot R, Boyle E, Gressin R, Nicolas-Virelizier E, Barrie M, Molucon-Chabrot C, Lelez ML, Clavert A, Coisy S, Leruez S, Touitou V, Cassoux N, 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. https://doi.org/10.1016/j.ejca.2019.05.024

This paper describes the role of Bruton's tyrosine kinase in PCNSL and early clinical experience with the use of ibrutinib monotherapy in treatment of relapsed CNS lymphomas.

59. Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, Butman JA, Schmitz R, Yang Y, Cole DE, Melani C, Higham CS, Desai JV, Ceribelli M, Chen L, Thomas CJ, Little RF, Gea-Banacloche J, Bhaumik S, Stetler-Stevenson M, Pittaluga S, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell. 2017;31(6):833–43 e835. https://doi.org/10.1016/j.ccell.2017.04.012.

60. Grommes C, Tang SS, Wolfe J, Kaley TJ, Daras M, Pentsova EI, Piotrowski AF, Stone J, Lin A, Nolan CP, Manne M, Codega P, Campos C, Viale A, Thomas AA, Berger MF, Hatzoglou V, Reiner AS, Panageas KS, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. Blood. 2019;133(5):436–45. https://doi.org/10.1182/blood-2018-09-875732.

61. Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-hodgkin lymphoma. J Clin Oncol. 2015;33(25):2803–11. https://doi.org/10.1200/JCO.2014.59.5363.

62. Rubenstein JL, Geng H, Fraser EJ, Formaker P, Chen L, Sharma J, Killea P, Choi K, Ventura J, Kurhanewicz J, Lowell C, Hwang J, Treseler P, Sneed PK, Li J, Wang X, Chen N, Gangoiti J, Munster PN, Damato B. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. Blood Adv. 2018;2(13):1595–607. https://doi.org/10.1182/bloodadvances.2017014845.

63. Ghesquieres H, Chevrier M, Laadhari M, Chinot O, Choquet S, Molucon-Chabrot C, Beauchesne P, Gressin R, Morschhauser F, Schmitt A, Gyan E, Hoang-Xuan K, Nicolas-Virelizier E, Cassoux N, Touitou V, Le Garff-Tavernier M, Savignoni A, Turbiez I, Soumelis V, 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) dagger. Ann Oncol. 2019;30(4):621–8. https://doi.org/10.1093/annonc/mdz032.

64. Tun HW, Johnston PB, DeAngelis LM, Atherton PJ, Pederson LD, Koenig PA, Reeder CB, Omuro AMP, Schiff D, O'Neill B, Pulido J, Jaeckle KA, Grommes C, Witzig TE. Phase 1 study of pomalidomide and dexamethasone for relapsed/refractory primary CNS or vitreoretinal lymphoma. Blood. 2018;132(21):2240–8. https://doi.org/10.1182/blood-2018-02-835496.

65. Goy A, Ramchandren R, Ghosh N, Munoz J, Morgan DS, Dang NH, Knapp M, Delioukina M, Kingsley E, Ping J, Beaupre DM, Neuenburg JK, Ruan J. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. Blood. 2019;134(13):1024–36. https://doi.org/10.1182/blood.2018891598.

66. El-Galaly TC, Cheah CY, Bendtsen MD, Nowakowski GS, Kansara R, Savage KJ, Connors JM, Sehn LH, Goldschmidt N, Shaulov A, Farooq U, Link BK, Ferreri AJM, Calimeri T, Cecchetti C, Dann EJ, Thompson CA, Inbar T, Maurer MJ, et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. Eur J Cancer. 2018;93:57–68. https://doi.org/10.1016/j.ejca.2018.01.073.

67. Narita Y, Nagane M, Mishima K, Terui Y, Arakawa Y, Yonezawa H, Asai K, Fukuhara N, Sugiyama K, Shinojima N, Kitagawa J, Aoi A, Nishikawa R. Phase I/II study of tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory primary central nervous system lymphoma. Neuro-Oncology. 2021;23(1):122–33. https://doi.org/10.1093/neuonc/noaa145.

68. Takashima Y, Hayano A, Yamanaka R. Metabolome analysis reveals excessive glycolysis via PI3K/AKT/mTOR and RAS/MAPK signaling in methotrexate-resistant primary CNS lymphoma-derived cells. Clin Cancer Res. 2020;26(11):2754–66. https://doi.org/10.1158/1078-0432.CCR-18-3851.

69. Korfel A, Schlegel U, Herrlinger U, Dreyling M, Schmidt C, von Baumgarten L, Pezzutto A, Grobosch T, Kebir S, Thiel E, Martus P, Kiewe P. Phase II trial of temsirolimus for relapsed/refractory primary CNS lymphoma. J Clin Oncol. 2016;34(15):1757–63. https://doi.org/10.1200/JCO.2015.64.9897.

70. Grommes CPE, Nolan C, Wolfe J, Mellinghoff IK, Deangelis L. Phase II study of single agent buparlisib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL). Ann Oncol. 2016;27(suppl 6):335.

71. Ou A, Sumrall A, Phuphanich S, Spetzler D, Gatalica Z, Xiu J, Michelhaugh S, Brenner A, Pandey M, Kesari S, Korn WM, Mittal S, Westin J, Heimberger AB. Primary CNS lymphoma commonly expresses immune response biomarkers. Neurooncol Adv. 2020;2(1):vdaa018. https://doi.org/10.1093/noajnl/vdaa018.

72. Furuse M, Kuwabara H, Ikeda N, Hattori Y, Ichikawa T, Kagawa N, Kikuta K, Tamai S, Nakada M, Wakabayashi T, Wanibuchi M, Kuroiwa T, Hirose Y, Miyatake SI. PD-L1 and PD-L2 expression in the tumor

microenvironment including peritumoral tissue in primary central nervous system lymphoma. BMC Cancer. 2020;20(1):277. https://doi.org/10.1186/s12885-020-06755-y.

73. El-Tawab R, Hamada A, Elhagracy R, Pinto K, Alshemmari S. Promising effect of PDL1 inhibitors in the front-line management of primary aggressive central nervous system lymphoma: a case report. Hematol Oncol Stem Cell Ther. 2020. https://doi.org/10.1016/j.hemonc.2020.06.003.
74. Nayak L, Iwamoto FM, LaCasce A, Mukundan S, Roemer MGM, Chapuy B, Armand P, Rodig SJ, Shipp MA. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood. 2017;129(23):3071–3. https://doi.org/10.1182/blood-2017-01-764209.
75. Frigault MJ, Dietrich J, Martinez-Lage M, Leick M, Choi BD, DeFilipp Z, Chen YB, Abramson J, Crombie J, Armand P, Nayak L, Panzini C, Riley LS, Gallagher K, Maus MV. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019;134(11):860–6. https://doi.org/10.1182/blood.2019001694.
76. Bennani NNMM, Nastoupil LJ, Jain MD, Chavez JC, Cashen AF, et al. Experience with axicabtagene ciloleucel (Axi-cel) in patients with secondary cns involvement: results from the US lymphoma CAR T consortium. Blood. 2019;134:763.
77. Ghafouri S, Timmerman J, Larson S, Mead MD. Axicabtagene ciloleucel CAR T-cell therapy for relapsed/refractory secondary CNS non-Hodgkin lymphoma: comparable outcomes and toxicities, but shorter remissions may warrant alternative consolidative strategies? Bone Marrow Transplant. 2021;56(4):974–7. https://doi.org/10.1038/s41409-020-01099-4.
78. Abramson JS, McGree B, Noyes S, Plummer S, Wong C, Chen YB, Palmer E, Albertson T, Ferry JA, Arrillaga-Romany IC. Anti-CD19 CAR T cells in CNS diffuse large-B-cell lymphoma. N Engl J Med. 2017;377(8):783–4. https://doi.org/10.1056/NEJMc1704610.
79. Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M, Yang JC, Phan GQ, Hughes MS, Sherry RM, Raffeld M, Feldman S, Lu L, Li YF, Ngo LT, Goy A, Feldman T, Spaner DE, Wang ML, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol. 2015;33(6):540–9. https://doi.org/10.1200/JCO.2014.56.2025.
80. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Chew A, Hauck B, Wright JF, Milone MC, Levine BL, June CH. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368(16):1509–18. https://doi.org/10.1056/NEJMoa1215134.
81. Tu S, Zhou X, Guo Z, Huang R, Yue C, He Y, Li M, Chen Y, Liu Y, Chang LJ, Li Y. 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. https://doi.org/10.3389/fonc.2019.01350.
82. Bairey O, Siegal T. The possible role of maintenance treatment for primary central nervous system lymphoma. Blood Rev. 2018;32(5):378–86. https://doi.org/10.1016/j.blre.2018.03.003.
83. Faivre G, Butler MJ, Le I, Brenner A. Temozolomide as a single agent maintenance therapy in elderly patients with primary CNS lymphoma. Clin Lymphoma Myeloma Leuk. 2019;19(10):665–9. https://doi.org/10.1016/j.clml.2019.05.012.
84. Pulczynski EJ, Kuittinen O, Erlanson M, Hagberg H, Fossa A, Eriksson M, Nordstrom M, Ostenstad B, Fluge O, Leppa S, Fiirgaard B, Bersvendsen H, Fagerli UM. Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group. Haematologica. 2015;100(4):534–40. https://doi.org/10.3324/haematol.2014.108472.
85. Fritsch K, Kasenda B, Schorb E, Hau P, Bloehdorn J, Mohle R, Low S, Binder M, Atta J, Keller U, Wolf HH, Krause SW, Hess G, Naumann R, Sasse S, Hirt C, Lamprecht M, Martens U, Morgner A, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). Leukemia. 2017;31(4):846–52. https://doi.org/10.1038/leu.2016.334.
86. Mishima K, Shirahata M, Adachi J, Suzuki T, Fujimaki T, Nishikawa R. P14.113 The role of maintenance high-dose methotrexate chemotherapy in elderly primary CNS lymphoma patients with complete response to induction immunochemotherapy. Neuro-Oncology. 2019;21(Supplement_3):iii95-iii95. https://doi.org/10.1093/neuonc/noz126.348.
87. Vu K, Mannis G, Hwang J, Geng H, Rubenstein JL. Low-dose lenalidomide maintenance after induction therapy in older patients with primary central nervous system lymphoma. Br J Haematol. 2019;186(1):180–3. https://doi.org/10.1111/bjh.15787.
88. Khurana A, Al-Juhaishi T, Yazbeck V, Shafer D. Primary ocular lymphoma: a SEER database analysis of patterns of involvement and outcomes. Blood. 2019;134(Supplement_1):4013-4013. https://doi.org/10.1182/blood-2019-132011.
89. Calimeri TS, Batchelor S, T. Innovative therapeutic strategies for primary CNS lymphoma. Curr Treat Options Neurol. 2021;23:12.
90. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, Smith JR, Korfel A, Soussain C, LM DA, Neuwelt EA, O'Neill BP, Thiel E, Shenkier T, Graus F, van den Bent M, Seymour JF, Poortmans P, Armitage JO, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol.

2005;23(22):5034–43. https://doi.org/10.1200/JCO.2005.13.524.
91. Re A, Cattaneo C, Rossi G. HIV and lymphoma: from epidemiology to clinical management. Mediterr J Hematol Infect Dis. 2019;11(1):e2019004. https://doi.org/10.4084/MJHID.2019.004.
92. Moulignier A, Lamirel C, Picard H, Lebrette MG, Amiel C, Hamidi M, Polivka M, Mikol J, Cochereau I, Pialoux G. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. Neurology. 2017;89(8):796–804. https://doi.org/10.1212/WNL.0000000000004265.
93. O'Neill A, Mikesch K, Fritsch K, Kasenda B, Banerjee L, Burns F, Zakout G, Johnston R, Illerhaus G, Cwynarski K. Outcomes for HIV-positive patients with primary central nervous system lymphoma after high-dose chemotherapy and auto-SCT. Bone Marrow Transplant. 2015;50(7):999–1000. https://doi.org/10.1038/bmt.2015.18.
94. Olszewski AJ, Fallah J, Castillo JJ. Human immunodeficiency virus-associated lymphomas in the antiretroviral therapy era: analysis of the National Cancer Data Base. Cancer. 2016;122(17):2689–97. https://doi.org/10.1002/cncr.30112.

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