Chapter 8
Novel Agents in Primary Central Nervous System Lymphoma

Raghuveer Ranganathan and Natalie Sophia Grover

Introduction

Primary central nervous system lymphoma (PCNSL) is an uncommon subclass of extranodal non-Hodgkin lymphoma (NHL) that can occur in the brain, cerebrospinal fluid (CSF), spinal column, or eyes, in the absence of systemic disease. It has an archetypally aggressive clinical phenotype but is chemo- and radiosensitive. However, it tends to have inferior survival compared to systemic lymphomas, with relapsed and refractory disease having especially abysmal long-term outcomes. Though there are several widely used therapeutic regimens, there is no accepted standard for PCNSL treatment, and the disease continues to be a challenge clinically. However, there has been progress in the utilization of novel agents and cellular immunotherapies, which show clinical promise. After a brief review of the most current treatment regimens, this chapter will explore the ongoing studies with novel therapeutic modalities addressing PCNSL.

Epidemiology

PCNSL accounts for approximately 3% of newly diagnosed CNS tumors and 5% of extranodal lymphomas, with about 1200 new cases per year arising in the United States [1, 2]. It is an AIDS-defining illness, and its overall incidence increased during the AIDS epidemic from the mid-1980s to the mid-1990s but has since decreased [2]. Since the year 2000, the demographics of PCNSL have changed, and incidence in

R. Ranganathan · N. S. Grover (✉)
Department of Medicine, Division of Hematology and Oncology,
University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
e-mail: raghuveer.ranganathan@unchealth.unc.edu; natalie_grover@med.unc.edu

C. Dittus (ed.), *Novel Therapeutics for Rare Lymphomas*,
https://doi.org/10.1007/978-3-030-25610-4_8

patients aged 65 and older has increased, particularly in those patients older than 75 years of age [2]. Median age at diagnosis is between 61 and 65.

Clinical Presentation

PCNSL patients can present with a constellation of neurologic symptoms. Focal neurologic deficits (~70%), neuropsychiatric changes (~43%), and nausea, headaches, and vomiting associated with increased intracranial pressure (33%) are the primary presenting symptoms [3]. Neuropsychiatric changes can present as behavioral or mental status changes. Seizures are a somewhat infrequent manifestation, occurring less than 15% of the time. Twenty percent of PCNSL develop in, or eventually involve, the eyes, with primary complaints being vision changes, vitreous floaters, or even complete blindness [4]. Seven to forty-two percent of PCNSL patients have morphological CSF involvement, while primary meningeal involvement without concurrent parenchymal evidence of disease is very rare (7% of cases) [5–7].

Diagnosis and Workup

Neuroimaging with magnetic resonance imaging (MRI) is the accepted gold standard imaging modality [8, 9]. MRI with and without contrast of the brain, ophthalmologic evaluation, and CSF examination by lumbar puncture are the standard elements of the initial workup [9]. MRI of the spine can be completed if spinal involvement is suspected. Nearly 70% of immunocompetent PCNSL patients present with a solitary, homogenously enhancing brain lesion on T1-weighted MRI imaging, while 30% have multiple lesions; both presentations are usually accompanied by varying degrees of surrounding vasogenic edema [10]. Up to a quarter of PCNSL tumors are associated with separate, non-enhancing lesions that are hyperintense on T2 fluid-attenuated inversion recovery (FLAIR)-weighted imaging, which points to promulgation of the lymphoma [11, 12]. Due to their high cellularity, PCNSL also display hyperintensity on diffusion-weighted imaging and hypointensity on apparent diffusion coefficient valuations [13]. On retrospective analysis, close to 90% of PCNSL tumors are found in a supratentorial location, with the most common lesion sites being the frontal lobe, parietal lobe, temporal lobe, basal ganglia, corpus callosum, and cerebellum [3].

Histopathological confirmation is compulsory and usually requires a sample of the affected brain tissue. A stereotactic biopsy is the procedure of choice. Steroid pretreatment is often given to alleviate symptoms from the tumor but should be delayed, if possible, until after the biopsy has been collected, as it can lead to decreased sensitivity and specificity of biopsy results. However, in the setting of unstable neurologic status, steroid use is sometimes unavoidable and should be implemented to reduce the risk of neurologic complications and sequelae.

In addition to pathological confirmation, 5–10 mL of CSF by lumbar puncture should be collected either 1 week before or after surgical biopsy to reduce risk of false-positive results. The CSF should be examined for cytology, flow cytometry, cell count, and protein. In some cases, if CSF is diagnostic of PCNSL, brain biopsy may be deferred.

Between 4% and 8% of patients initially thought to have PCNSL end up having systemic occult disease, so a PET CT or CT with contrast should be done to rule out systemic lymphoma [14]. Ophthalmologic evaluation usually includes fundoscopy and slit lamp examination. Testicular exam as part of the overall physical exam is also warranted to rule out testicular lymphoma as the primary cause for CNS disease. All patients' HIV status should be confirmed, and antiretroviral therapy should be initiated in HIV patients not already on therapy.

Pathology

The majority of PCNSL are of the diffuse large B cell lymphoma (DLBCL) subtype [15]. However, there are occasional cases of T-cell lymphoma [16], Hodgkin lymphoma [17], and low-grade lymphomas [18]. This chapter will focus on the DLBCL subtype.

Prognosis

Two scoring systems are used to stratify the prognosis of PCNSL: the International Extranodal Lymphoma Study Group (IELSG) and the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic scores. The IELSG score is based on five risk factors: age above 60 years, Eastern Cooperative Oncology Group performance status above 1, elevated LDH, elevated CSF protein, and whether the tumor arises within the deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum) [19]. The 2-year overall survival (OS) rates were 80%, 48%, and 15% for patients having zero to one, two to three, and four to five of the risk factors, respectively. The MSKCC score has two characteristics: age and Karnofsky Performance Score (KPS). Patients are divided into three prognostic groups: age ≤ 50 plus KPS ≥ 70, age > 50 plus KPS ≥ 70, and age > 50 plus KPS < 70. These groups correspond to median OS of 5.2, 2.1, and 0.9 years, respectively.

Conventional Treatment

A major problem with the treatment of PCNSL is that no unanimity on the ideal therapeutic approach exists. This is primarily due to the lack of randomized studies comparing different regimens because of the rarity of the disease. Additionally,

there is difficulty enrolling patients with PCNSL on clinical trials, due to their frequent poor performance status at diagnosis. However, over the past two decades, certain requisite elements have been identified and form the basis for modern PCNSL therapy.

Historically, treatment of PCNSL was solely dependent on whole-brain radiation (WBRT) with doses of 45–51 Gy; while the overall response rates (ORR) were high, the ensuing median OS was only 1–1.5 years with a 5-year survival of 25% [20–23]. The high doses of WBRT also resulted in debilitating neurotoxicity, especially in patients older than 60 years of age. Targeted radiation to just the tumor involved areas of the brain demonstrated increased relapse rates in the regions that were not radiated [22, 23]. Traditional chemotherapy regimens used for systemic DLBCL, when combined with WBRT, did not show adequate efficacy for PCNSL due to low penetration of the blood-brain barrier (BBB) [23–25].

High-dose methotrexate (HD-MTX) (at doses >1.0 g/m^2) has been used to treat other hematologic malignancies at high risk of CNS involvement or relapse, such as acute lymphoblastic leukemia [26–28]. While doses >1.0 g/m^2 yield therapeutic levels in the brain parenchyma, MTX doses >3.0 g/m^2 produce tumoricidal concentrations in the cerebrospinal fluid as well as brain parenchyma [29]. As a result, the majority of PCNSL chemotherapy regimens incorporate a HD-MTX dose >3.0 g/m^2 and up to 8 g/m^2 [5]. When combined with WBRT for PCNSL treatment, there was an improved OS rate compared to WBRT alone. In single-arm, phase II trials, HD-MTX plus WBRT showed similar ORR of 88–95% compared to historical controls of WBRT alone but with improved median OS of 33–42 months [30–32]. A seminal, randomized phase II trial by Ferreri and colleagues illustrated HD-MTX with cytarabine followed by WBRT showed better ORR and PFS than HD-MTX alone plus WBRT [33]. This finding led to additional polychemotherapy regimens being examined with WBRT or modifying consolidation strategies in lieu of WBRT due to concerns over long-term neurocognitive toxicity with radiation. Since rituximab greatly enhances efficacy in systemic, non-CNS DLBCL, it was included in many PCNSL treatment regimens. The Cancer and Leukemia Group B (CALGB) 50202 single-arm study treated newly diagnosed PCNSL patients with an induction regimen of rituximab, HD-MTX, and the alkylating agent temozolomide (R-MT) followed by consolidation with cytarabine plus etoposide and omitting WBRT altogether. The ORR was 77%, with a CR rate of 66% and 2-year PFS and time to progression (TTP) of 57% and 59%, respectively; those patients who completed consolidation had a 2-year TTP of 77% and estimated 4-year OS of 65% [34]. The Radiation Therapy Oncology Group (RTOG) 0227 phase I/II study also looked at induction therapy with R-MT but added consolidation with WBRT and maintenance temozolomide following radiation. The induction alone resulted in ORR 84% with CR rate of 51%; after completion of induction and consolidation, 2-year PFS and OS were 64% and 81%, respectively, with an estimated median PFS and OS of 5.4 years and 7.5 years, respectively [35].

Concerns with the neurocognitive toxicity from WBRT-containing treatment regimens, which became more apparent with the improving survival of PCNSL patients, prompted trials investigating decreasing the radiation doses or possibly circumventing the need for it completely. The aforementioned CALGB 50,202 study included consolidation with chemotherapy alone and excluded WBRT. A

multicenter phase II study evaluated the effectiveness of combining induction rituximab, HD-MTX, procarbazine, and vincristine (R-MPV) with reduced WBRT consolidation with a dose of 23.4 Gy. Induction therapy alone resulted in an ORR of 97% and CR of 47% (increased to 79% after patients with a PR were given two additional R-MPV cycles); 2-year PFS was 77% and 5-year OS was 80% [36]. The median PFS for all patients was 7.7 years, with the median PFS in patients ≤60 years of age not being reached. The median OS was not reached for patients regardless of age category. Importantly, with the reduced WBRT dose, there was less neurocognitive decline or deterioration among the evaluable patients.

One of the largest randomized trials comparing different induction and consolidation regimens was a phase II study by the IELSG32 group, which randomized the combination of the alkylating agent thiotepa with rituximab, HD-MTX, and cytarabine (MATRix) against HD-MTX plus cytarabine with or without rituximab for induction [37]. There was an additional randomization arm for investigating autologous stem cell transplant (auto-SCT) versus WBRT as consolidation. The MATRix regimen showed ORR of 87%, with CR of 49% compared to CR rates of 23% and 30% with the HD-MTX plus cytarabine with and without rituximab arms, respectively. The 2-year PFS and OS for MATRix was 61% and 69%, respectively. The second randomization arm for consolidation demonstrated no significant differences in outcomes; the 2-year PFS was 76% for WBRT and 75% for auto-SCT, with a 4-year OS of 85% versus 83% for WBRT and auto-SCT, respectively [38]. A phase II study examining auto-SCT following R-MPV induction showed both a 2-year PFS and OS of 81% post-transplant [39]. Subsequent studies with auto-SCT suggest that a standard conditioning regimen like BEAM (BCNU, etoposide, cytarabine, melphalan) does not have good efficacy due to decreased penetration of the BBB [40, 41]. Two thiotepa-containing regimens, thiotepa plus busulfan and cyclophosphamide as well as thiotepa with BCNU, show excellent efficacy due to their CNS bioavailability with the BCNU-thiotepa regimen showing lower toxicities, better tolerance, and less patient mortality compared to thiotepa-busulfan-cyclophosphamide (TBC) [40, 42–45].

Though there is no accepted standard regimen for PCNSL therapy, the results from these trials strongly suggest that PCNSL treatment should consist of an induction phase followed by consolidative therapy. The induction backbone should comprise HD-MTX (>3 g/m^2), alkylating agents, and likely rituximab for a polychemotherapeutic approach. Consolidation could consist of either WBRT and chemotherapy or auto-SCT. The induction treatment regimens exhibiting efficacy with minimal neurotoxicities or patient morbidity/mortality are R-MPV and MATRix. Induction should be followed by consolidation with either reduced-dose WBRT or auto-SCT with BCNU-thiotepa conditioning appearing to be better tolerated than TBC.

Relapsed/Refractory PCNSL

Although the prognosis of PCNSL has improved with the incorporation of HD-MTX-based regimens and consolidation therapy, there is still a substantial

proportion of patients with relapsed or refractory disease. Unfortunately, treatment options for patients with recurrent or progressive disease are limited. Patients who did not get radiation up front may be treated with WBRT at time of relapse. Patients with a response duration greater than 1 year may be retreated with HD-MTX [8, 46]. Patients are also considered for other systemic chemotherapy options including temozolomide [47], high-dose cytarabine [48], topotecan [49], and pemetrexed [50], which have modest efficacy and brief duration of response. Novel therapeutic agents are urgently needed for this disease.

Basis for Novel Agents

Pathophysiologic findings and gene-expression profiles reveal unique features for the possible pathogenesis of PCNSL (Fig. 8.1). Immunophenotypically, PCNSL is predominantly of the activated B cell (ABC) classification, based on the expression of MUM-1 and BCL-6 [51]. NFκB, a protein complex involved with controlling DNA transcription and promoting cell survival and proliferation, has been shown to be constitutively active and required for blocking apoptosis in ABC-DLBCL subtypes [52]. Mutations affecting proteins which regulate NFκB also result in increased activation of NFκB [53]. MYD88, an intracellular adapter protein, is a commonly mutated target in PCNSL, affecting more than half of PCNSL cases. It actuates NFκB through interleukin-1 receptor-associated kinases (IRAKs). Activating mutations in MYD88 result in upregulation of IRAK activity and, consequently, NFκB. CD79B, a B cell receptor (BCR)-associated protein, is a second frequently mutated target in PCNSL. Other proteins that are implicated in the dysregulation of NFκB activation include CARD11 and TNFAIP3 (an inhibitory mediator of NFκB) [54]. Critically, chronic BCR signaling through BCR clustering and utilization of BCR-related kinases such as SYK or Bruton's tyrosine kinase (BTK) can also promote survival of PCNSL [55]. Additional pro-survival circuits harnessed by PCNSL are the PI3K/mTOR and JAK/STAT pathways and increased copy number gains of the chromosomal locus 9p24.1, which correlates with increased PDL1 expression. This preponderance of mutational and dysregulatory aberrations has been a primary reason for the study of new immunotherapeutic and immunomodulatory agents in PCNSL.

Ibrutinib

Due to the high incidence of BCR pathway aberrations, ibrutinib has become an attractive novel agent to investigate in PCNSL. It is an oral inhibitor of BTK that has gained significant attention as a therapeutic modality in NHL. The ABC subtype of DLBCL shows a dependence upon BTK for survival, and blocking the kinase can

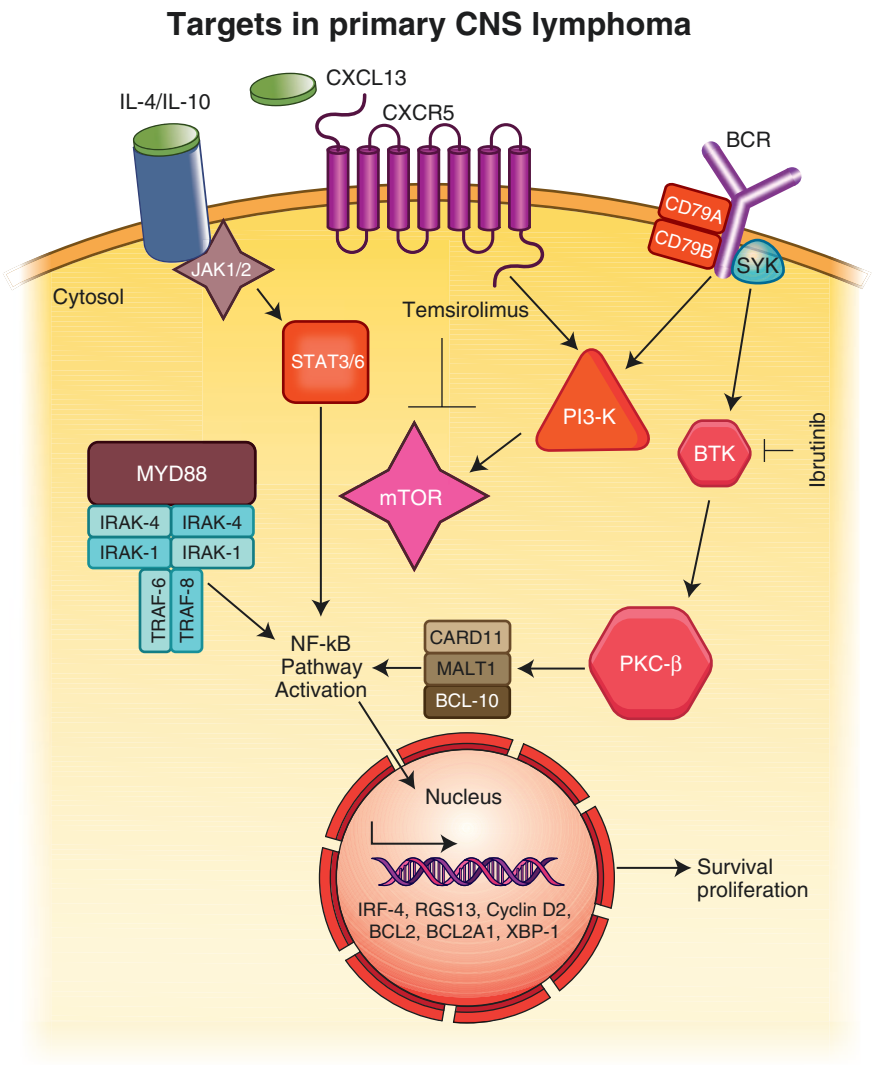

Fig. 8.1 Targets in primary CNS lymphoma. The activation of NF-κB allows for survival and proliferation of PCNSL tumor cells and is controlled by a myriad of signalling pathways. Some novel agents target these pathways. Blocking Bruton's tyrosine kinase (BTK), which acts downstream from the B cell receptor (BCR), is the primary mode of action for ibrutinib. Close to 60% of PCNSL cases harbor the L265P mutation in MYD88, resulting in constitutive activity of IRAK kinases and subsequent NF-κB-dependent transcription of pro-survival genes such as BCL-2, IRF-4, etc. Temsirolimus inhibits the mTOR pathway, which is another pro-survival pathway

instigate apoptosis [55, 56]. A phase I/II clinical trial in 80 patients with relapsed/refractory DLBCL receiving ibrutinib showed an ORR of 25% with CR of 10%, with a relatively short PFS and OS of 1.64 and 6.41 months, respectively [56]. However, in the subset of patients with ABC-DLBCL, there was a notable increased response with ORR of 37% and CR of 16%, with a PFS and OS of 2.02 and 10.35 months, respectively. The ABC-DLBCLs that had BCR mutations in CD79B with concurrent MYD88 mutations exhibited favorable responses of 55%; interestingly, the highest rate of response occurred in ABC patients who had wild-type BCR, suggesting non-genetic processes can be the driving force for oncogenesis. A small case series involving three mantle cell lymphoma patients having relapsed disease in the CNS showed two CRs and one PR at 6–12-month follow-up, with confirmation of CNS penetration by ibrutinib through CSF analysis of the patients [57].

One of the first PCNSL studies with ibrutinib was a non-randomized, single-center phase I trial with 20 relapsed/refractory CNS lymphoma patients [58]. Thirteen had PCNSL, while seven had secondary CNS involvement from systemic DLBCL (SCNSL); all of them had received HD-MTX-based chemotherapy prior to enrollment. Of the 13 PCNSL patients, 10 patients or 77% showed a clinical response, with a CR in 5 patients (38%). The three patients who had malignant cells detected in the CSF had no lymphoma cells detected during follow-up evaluations. After a median follow-up of 15.5 months, the median PFS and OS were 4.6 and 15 months, respectively. Sixty percent of patients who had been receiving steroids for symptomatic relief prior to ibrutinib were able to be tapered off the steroids once therapy was initiated. Overall, ibrutinib was well tolerated with the most commonly observed adverse effects being grade 1–2: hyperglycemia (80%), anemia and/or thrombocytopenia (60–65%), hypercholesterolemia and/or hypertriglyceridemia (60–65%), and hypoalbuminemia or AST elevation (40–50%). Grade 3–4 toxicities involved neutropenia in 15%, with febrile neutropenia occurring in 5%. These abnormalities resolved with the drug being held temporarily. One patient, however, had to be permanently taken off ibrutinib due to pulmonary aspergillosis. Among the tumors that had genomic analyses, mutations in CARD11 appeared to be a harbinger of partial or complete resistance to ibrutinib. Unexpectedly, none of the PCNSL patients with concomitant MYD88 and CD79B mutations showed a CR, which is contradictory to reported responses in systemic ABC-DLBCL.

A prospective, multicenter, open-label phase II trial enrolled 52 patients with either relapsed/refractory PCNSL or primary vitreoretinal lymphoma (PVRL), who were administered ibrutinib monotherapy at 560 mg until disease progression or adverse toxicity [59]. Concurrent steroid use was allowed during the initial 4 weeks for symptomatic cerebral edema. All the patients had exposure to HD-MTX-based chemotherapy prior to the trial, with four patients having auto-SCT as consolidation. An interim analysis after 2 months of treatment revealed an ORR of 55.6%, with CR of 16.7%. One patient developed pulmonary aspergillosis but recovered, and no treatment-related mortality overall was reported up to the time of interim analysis.

Since ibrutinib monotherapy showed modest PFS results, approaches incorporating it with chemotherapy were examined in a phase Ib study. In this trial, ibrutinib

monotherapy was initiated for 2 weeks, followed by a polychemotherapy-ibrutinib combination with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab, and ibrutinib (TEDDi-R) [60]. Liposomal doxorubicin was incorporated into the regimen because non-liposomal doxorubicin does not penetrate the blood-brain barrier (BBB). Using in vitro assays with ABC-DLBCL cell lines, the investigators noted anti-folate agents such as HD-MTX showed antagonism when implemented concurrently with ibrutinib, while the chemotherapy agents included in the final TEDDi-R regimen showed high synergistic action with ibrutinib. Eighteen patients with PCNSL were enrolled in the study; thirteen of whom were relapsed/refractory and five were newly diagnosed. All patients were treated at ibrutinib dose levels of 560, 700, or 800 mg for 2 weeks. Two patients developed grade 5 pulmonary/CNS aspergillosis during the ibrutinib lead-in period, while the remaining 16 patients proceeded to receive TEDDi-R chemotherapy. There was an ORR of 94% (17/18) on ibrutinib monotherapy alone, with two relapsed/refractory patients eventually achieving CR. Twenty-two percent of patients with CSF involvement became negative by flow cytometry on monotherapy. There was an 86% CR rate in the patients who received TEDDi-R, with median PFS of 15.5 months and median OS that was not reached. However, 39% of patients contracted invasive pulmonary/CNS aspergillosis infections during the trial. Two patients died from aspergillosis during the ibrutinib monotherapy phase, while five cases of aspergillosis infections occurred during the TEDDi-R treatment. A patient also died from neutropenic sepsis while receiving TEDDi-R. In contrast, PCNSL treatment-related mortality with conventional chemotherapy and consolidation modalities is quite low at 1–8% [61]. In addition, 56% developed grade 4 thrombocytopenia and 94% had grade 4 neutropenia. The authors cited their preclinical studies showing more susceptibility to *Aspergillus fumigatus* exposure in mice lacking BTK compared to those with wild-type BTK. Their findings suggested that BTK plays a role as part of macrophage and neutrophil response mechanisms to control aspergillosis infections and initiate adaptive immunity. Corticosteroid use with dexamethasone as part of the regimen with ibrutinib was also mentioned as a possible contributory factor. However, previous trials with ibrutinib monotherapy had patients taking concurrent steroids with ibrutinib and reported a much lower occurrence of aspergillosis infection [58, 59]. Nevertheless, if ibrutinib continues to show promise as a therapeutic adjunct for PCNSL treatment, fungal prophylaxis may need to be incorporated with ibrutinib treatment.

Future directions of ibrutinib in PCNSL involve designing combinations that can lead to more durable responses while maintaining a good safety profile. An ongoing clinical trial is investigating the combination of ibrutinib with HD-MTX and rituximab in patients with relapsed or refractory PCNSL and SCNSL (NCT02315326) (Table 8.1). In this trial, to avoid interactions, ibrutinib is stopped on the day of HD-MTX infusion and only restarted 5 days after HD-MTX or at time of clearance. Preliminary results suggest that this combination is tolerable but enrollment is ongoing [62]. Another clinical trial is evaluating the role of ibrutinib as maintenance in elderly patients with PCNSL after induction with a polychemotherapy regimen of rituximab, methotrexate, and another agent (NCT02623010) (Table 8.1).

Table 8.1 Active clinical trials for primary CNS lymphoma

Clinicaltrials.gov identifier	Drug	Design/concept
NCT02315326	Ibrutinib	Phase 1/2 trial in relapsed/refractory primary and secondary CNS lymphoma
		One arm investigating combination of high-dose methotrexate and ibrutinib
NCT02623010	Ibrutinib	Studying maintenance ibrutinib in elderly (age 60–85) patients with primary CNS lymphoma
		Patients initially receive induction with rituximab and high-dose methotrexate protocol and patients with response will receive maintenance ibrutinib until relapse or disease progression
NCT02857426	Nivolumab	Phase 2 trial of nivolumab in relapsed/refractory primary CNS lymphoma or primary testicular lymphoma
NCT02779101	Pembrolizumab	Phase 2 trial of pembrolizumab in relapsed/refractory primary CNS lymphoma
NCT03255018	Pembrolizumab	Phase 2 trial of pembrolizumab in relapsed/refractory gray-zone lymphoma, primary CNS lymphoma, and other extranodal DLBCL
NCT03212807	Durvalumab and lenalidomide	Phase 2 trial of durvalumab and lenalidomide in relapsed/refractor primary CNS lymphoma and other types of DLBCL
NCT02669511	PQR309	Phase 2 trial of PQR309, PI3K, and mTOR inhibitor, in patients with relapsed/refractory primary CNS lymphoma
NCT02498951	Obinutuzumab	Randomized trial studying maintenance obinutuzumab in patients who achieved complete response to first-line treatment with high-dose methotrexate-based chemotherapy
		Patients are randomized to obinutuzumab every 60 days for 2 years or until progression or observation

Ibrutinib appears to have high response rates but suboptimal duration of response as a single agent in PCNSL. We await results of combination studies that may improve the efficacy of ibrutinib, as well as further clarify the toxicity profile.

Checkpoint Inhibitors

PD-1 is an inhibitory receptor expressed by activated T cells on the cell surface. Its ligands, PD-L1 and PD-L2, are upregulated in expression in many cancers. Evidence of increased expression of the PD-1/PD-L1 signaling pathway in PCNSL has spawned interest in checkpoint inhibition as an investigative modality. PD-L1 overexpression, while a relatively uncommon feature in NHL, happens in subsets of

ABC-DLBCL [63], which is the most frequently seen subtype in PCNSL. PD-1 checkpoint inhibitors have shown efficacy in heavily pretreated DLBCL in a phase I trial [64]. PCNSL has been noted to have increased PD-L1 expression secondary to chromosomal gains at the 9p24.1 genetic locus, which contains the PD-L1/PD-L2 genes [54, 65]. The presence of reactive, perivascular T cell infiltrates at PCNSL tumor sites has been shown to correlate with a survival benefit [65]. This suggests that PD-1/PD-L1 checkpoint inhibition could augment this survival advantage by thwarting the immunosuppression imparted by the PD-1/PD-L1 axis upon the reactive T cells.

Nivolumab and pembrolizumab are both anti-PD-1, humanized IgG4 antibodies which have FDA approval for use in many solid malignancies such as melanoma, renal cell, and non-small cell lung cancers. Both immunotherapies are also being actively studied in hematologic malignancies that show PD-L1 overexpression and have been FDA approved for the treatment of Hodgkin lymphoma. While investigation with these medications in PCNSL is in the nascent stages, PD-1 inhibition shows potential for clinical use. In a small pilot study of five patients, four with relapsed/refractory PCNSL and one with CNS relapse of primary testicular lymphoma (PTL), PD-1 blockade with nivolumab induced clinical responses in all five patients [66]. Among the four PCNSL patients, all achieved a CR, with two patients relapsing after 14 and 17 months, respectively. The remaining two patients were disease-free at the time of study publication (13 and 17 months, respectively). Nivolumab was relatively well-tolerated by the patients overall. The only significant complication involved one patient with a history of chronic renal insufficiency who developed renal failure requiring hemodialysis, which was not thought to be due to nivolumab. Currently there is an ongoing multicenter, phase II, single-arm study investigating nivolumab in relapsed/refractory PCNSL or PTL (NCT02857426). Additionally, there are two ongoing studies evaluating the use of pembrolizumab in PCNSLs. One is an ongoing, single-center, open-label, single-arm phase II study examining pembrolizumab use in recurrent PCNSL (NCT02779101); the other is a study investigating the use of pembrolizumab in extranodal lymphomas including PCNSL (NCT03255018) (Table 8.1). Although preliminary data on checkpoint inhibitors in PCNSL is very promising, we await further data to better clarify their role in the treatment of PCNSL.

Pomalidomide and Lenalidomide

Immunomodulatory imide drugs (IMiDs) such as pomalidomide and lenalidomide display particularly heightened cytotoxicity toward ABC-DLCBL tumor cells [67]. This is partly explained by their cereblon-mediated degradation of the MUM1/IRF4 transcription factor, a protein highly expressed in PCNSL [68]. IMiDs also synergistically boost the NK cell-driven antibody-dependent cellular cytotoxicity of rituximab [69]. The combination of lenalidomide with rituximab demonstrated efficacy in DLBCL in phase II trials [70, 71]. The same combination was tried in

PCNSL patients as a phase I trial, with the addition of lenalidomide maintenance following initial treatment. The rituximab was administered both intravenously and intraventricularly. Thirteen relapsed/refractory patients, eight with PCNSL and five with SCNSL, were recruited onto the study in total and given either 10, 20, or 30 mg dose levels. Preliminary results show 8 out of 13 patients achieving PR or better, with 4 CRs in patients with either parenchymal or intraocular disease [72]. At a median follow-up of >18 months, five patients had maintained remissions for >2 years. Ventricular CSF analysis also demonstrated CNS penetration by lenalidomide. The final results of the study are still pending with regards to PFS, OS, and adverse events.

A multicenter, phase II study, also looking at lenalidomide-rituximab, enrolled 50 patients with relapsed/refractory PCNSL or PVRL, all with prior exposure to HD-MTX therapies [73]. There was an induction phase of lenalidomide-rituximab, followed by lenalidomide maintenance. Interim analysis showed an ORR of 39% with a CR rate of 30% at the end of the induction phase. After a median follow-up of 9 months during the maintenance lenalidomide period, median PFS and OS were 8.1 and 15.3 months, respectively. Completed results of this investigation are forthcoming.

A phase I study combined pomalidomide, a second-generation IMiD, with dexamethasone in 25 relapsed/refractory PCNSL or PVRL patients [74]. Treatment consisted of pomalidomide at four-dose escalation levels for 21 out of 28 days with dexamethasone daily for two cycles, followed by pomalidomide alone for subsequent cycles until progression or toxicity. Interim analysis showed an ORR of 43% with CR of 24%. Grade 3/4 hematologic toxicities with either neutropenia, anemia, or thrombocytopenia occurred in 38% of patients, while non-hematologic toxicities of either fatigue, sepsis, rash, or respiratory issues happened in 33%.

With the molecular pathogenetic mechanisms of PCNSL bearing similarity to ABC-DLBCL and IMiDs showing viability as an effective second-line therapy, further studies are in progress to validate pomalidomide and lenalidomide use in PCNSL and PVRL. There is also an ongoing study investigating the combination of durvalumab (a PD-L1 inhibitor) with lenalidomide in relapsed or refractory PCNSL [NCT03212807] (Table 8.1).

Temsirolimus

The PI-3/AKT/mTOR signaling axis can be an additional pathway to promote anti-apoptotic behavior in PCNSL. Temsirolimus had previously been found to possess CNS penetrance at high concentrations within tumor specimens of malignant glioma patients [75]. A phase II study tested temsirolimus monotherapy in 37 relapsed/refractory PCNSL patients [76]. It exhibited an ORR of 56% with a CR rate of 21.5% and a median PFS of 2.1 months. However, a high degree of toxicity was observed, with an associated 13.5% treatment-associated mortality mostly from sepsis. There was also a question of whether cases of pneumonia were instead cases of pneumonitis, which is a well-known side effect of the drug. While temsirolimus

does show activity against PCNSL, its high rate of treatment-related mortality would likely make it a less desirable therapeutic option.

Chimeric Antigen Receptor T Cells

Chimeric antigen receptor T (CAR-T) cells genetically engineered to target CD19, an antigen found on most B cells, have shown significant promise in B cell malignancies including DLBCL and have recently been FDA approved for the treatment of relapsed or refractory DLBCL [77, 78]. However, studies of CAR-T cells have generally excluded patients with CNS involvement although it is known that CAR-T cells can cross the BBB and are found in patients' CSF [79, 80]. There was a recent case report published of a patient with refractory DLBCL with CNS relapse involving the brain parenchyma who was treated with CD19-directed CAR-T cells and achieved a CR which was durable with ongoing remission at 12 months [81]. Of course, more data is needed to make any conclusions, but this is encouraging and hopefully future studies will include some patients with CNSL.

Conclusion

While there has been recent incremental progress in PCNSL, especially in the frontline setting, there is still a poor prognosis in relapsed/refractory patients. It remains a difficult disease to study not only due to its rarity and, often, serious clinical presentation but also because many trials exclude patients with CNS involvement. However, novel agents offer promise for forthcoming treatments, especially in the relapsed/refractory setting. Though the studies are small, they offer potential avenues for improvement in PCNSL treatment. Future directions should focus on combining different novel immunotherapies with or without standard chemotherapy regimens that are currently used for PCNSL.

References

1. Hoffman SPJ, McCarthy BJ. Temporal trends in incidence of primary brain tumors in the United States, 1985–1999. Neuro-Oncology. 2006;8(1):27–37.
2. Villano JLKM, 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.
3. Bataille BDV, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. Neurosurgery. 2000;92(2):261–6.
4. Chan CC, Rubenstein J, Coupland SE, Davis JL, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16(11):1589–99.

5. Batchelor T, Carson K, O'Neill A, Grossman SA, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol. 2003;21(6):1044–9.
6. Jahnke K, Korfel A, Martus P, et al. High-dose methotrexate toxicity in elderly patients with primary central nervous system lymphoma. Ann Oncol. 2005;16(3):445–9.
7. Taylor JW, Flanagan E, O'Neill BP, Siegal T, et al. Primary leptomeningeal lymphoma: International Primary CNS Lymphoma Collaborative Group report. Neurology. 2013;81(19):1690–6.
8. Network NCC. Central nervous system cancers 2018. 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
9. Abrey LE, Batchelor T, Ferreri AJ, International Primary CNS Lymphoma Collaborative Group, 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.
10. Bühring U, Herrlinger U, Krings T, Thiex R, et al. MRI features of primary central nervous system lymphomas at presentation. Neurology. 2001;57(3):393–6.
11. Rubenstein JL. Biology of CNS lymphoma and the potential of novel agents. Hematol Am Soc Hematol Educ Program. 2017;1:556–64.
12. Tabouret E, Houillier C, Martin-Duverneuil N, et al. Patterns of response and relapse in primary CNS lymphomas after first-line chemotherapy: imaging analysis of the ANOCEF-GOELAMS prospective randomized trial. Neuro-Oncology. 2017;19(3):422–9.
13. Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. Am J Neuroradiol. 2010;32(6):984–92.
14. O'Neill BP, Dinapoli R, Kurtin PJ, et al. Occult systemic non-Hodgkin's lymphoma in patients initially diagnosed as primary central nervous system lymphoma: how much staging is enough? J Neuro-Oncol. 1995;25(1):67–71.
15. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma. The Massachusetts General Hospital experience 1958–1989. Cancer. 1994;74(4):1383–97.
16. Gijtenbeek JM, Rosenblum MK, DeAngelis LM. Primary central nervous system T-cell lymphoma. Neurology. 2001;57(4):716–8.
17. de Castro AF, Junior AS, de Lins e Horta H, Neuenschwander LC, Fonseca RP, Lima SS, et al. Primary intracerebral Hodgkin lymphoma. Br J Haematol. 2007;138(5):562.
18. Jahnke K, Korfel A, O'Neill BP, Blay JY, Abrey LE, Martus P, et al. International study on low-grade primary central nervous system lymphoma. Ann Neurol. 2006;59(5):755–62.
19. Ferreri AJ, Blay J, Reni M, Pasini F, et al. Prognostic scoring system for primary CNS lymphomas: The International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003;21(2):266–72.
20. Shibamoto Y, Ogino H, Hasegawa M, Suzuki K, et al. Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s. Int J Radiat Oncol Biol Phys. 2005;62(3):809–13.
21. Nelson DF, Martz K, Bonner H, Nelson JS, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys. 1992;23(1):9–17.
22. Shibamoto Y, Hayabuchi N, Hiratsuka J, et al. Is whole-brain irradiation necessary for primary central nervous system lymphoma? Patterns of recurrence after partial-brain irradiation. Cancer. 2003;97(1):128–33.
23. Grommes C, DeAngelis L. Primary CNS lymphoma. J Clin Oncol. 2017;35(21):2410–8.
24. Schultz C, Scott C, Sherman W, et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88-06. J Clin Oncol. 1996;14(2):556–64.
25. Mead GM, Bleehen N, Gregor A, Bullimore J, et al. A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and

without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer. 2000;89(6):1359–70.
26. Surapaneni UR, Cortes J, Thomas D, O'Brien S, et al. Central nervous system relapse in adults with acute lymphoblastic leukemia. Cancer. 2002;94(3):773–9.
27. Kantarjian HM, O'Brien S, Smith TL, Cortes J, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18(3):547–61.
28. Sancho JM, Ribera J, Oriol A, Hernandez-Rivas JM, et al. Central nervous system recurrence in adult patients with acute lymphoblastic leukemia: frequency and prognosis in 467 patients without cranial irradiation for prophylaxis. Cancer. 2006;106(12):2540–6.
29. Lippens RJ, Winograd B. Methotrexate concentration levels in the cerebrospinal fluid during high-dose methotrexate infusions: an unreliable prediction. Pediatr Hematol Oncol. 1988;5(2):115–24.
30. DeAngelis LM, Yahalom J, Thaler HT, Kher U, et al. Combined modality therapy for primary CNS lymphoma. J Clin Oncol. 1992;10(4):635–43.
31. O'Brien P, Roos D, Pratt G, Liew K, et al. Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. J Clin Oncol. 2000;18(3):519–26.
32. Glass J, Gruber M, Cher L, Hochberg FH. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. J Neurosurg. 1994;81(2):188–95.
33. Ferreri AJ, Reni M, Foppoli M, Martelli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet Oncol. 2009;374(9700):1512–20.
34. Rubenstein JL, Hsi E, Johnson JL, Jung SH, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 2013;31(25):3061–8.
35. Glass J, Won M, Schultz CJ, Brat D, et al. Phase I and II study of induction chemotherapy with methotrexate, rituximab, and temozolomide, followed by whole-brain radiotherapy and postirradiation temozolomide for primary CNS lymphoma: NRG oncology RTOG 0227. J Clin Oncol. 2016;34(14):1620–5.
36. Morris PG, Correa D, Yahalom J, Raizer JJ, et al. 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.
37. Ferreri AJ, Cwynarski K, Pulczynski E, Ponzoni M, 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(5):217–27.
38. Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy 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(11):510–23.
39. Omuro A, Correa D, DeAngelis LM, Moskowitz CH, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood. 2015;125(9):1403–10.
40. Ferreri AJ, Illerhaus G. The role of autologous stem cell transplantation in primary central nervous system lymphoma. Blood. 2016;127(13):1642–9.
41. Wiebe VJ, Smith B, DeGregorio MW, Rappeport JM. Pharmacology of agents used in bone marrow transplant conditioning regimens. Crit Rev Oncol Hematol. 1992;13(3):241–70.
42. Cote GM, Hochberg E, Muzikansky A, Hochberg FH, et al. Autologous stem cell transplantation with thiotepa, busulfan, and cyclophosphamide (TBC) conditioning in patients with CNS involvement by non-Hodgkin lymphoma. Biol Blood Marrow Transplant. 2012;18(1):76–83.
43. Cheng T, Forsyth P, Chaudhry A, Morris D, et al. High-dose thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain radiotherapy for poor prognosis primary CNS lymphoma. Bone Marrow Transplant. 2003;31(8):679–85.

44. Illerhaus G, Müller F, Feuerhake F, Schäfer AO, et al. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. Haematologica. 2008;93(1):147–8.
45. Bojic M, Berghoff A, Troch M, Agis H, et al. Haematopoietic stem cell transplantation for treatment of primary CNS lymphoma: single-centre experience and literature review. Eur J Haematol. 2015;95(1):75–82.
46. Network NCC. Central nervous system cancers: National Comprehensive Cancer Network. 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
47. 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.
48. Chamberlain MC. High-dose cytarabine salvage therapy for recurrent primary CNS lymphoma. J Neuro-Oncol. 2016;126(3):545–50.
49. Fischer L, Thiel E, Klasen HA, Birkmann J, Jahnke K, Martus P, et al. Prospective trial on topotecan salvage therapy in primary CNS lymphoma. Ann Oncol. 2006;17(7):1141–5.
50. Raizer JJ, Rademaker A, Evens AM, Rice L, Schwartz M, Chandler JP, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. Cancer. 2012;118(15):3743–8.
51. Camilleri-Broët S, Crinière E, Broët P, Delwail V, 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(1):190–6.
52. Davis RE, Brown K, Siebenlist U, Staudt LM. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med. 2001;194(12):1861–74.
53. Vlahopoulos SA. Aberrant control of NF-κB in cancer permits transcriptional and phenotypic plasticity, to curtail dependence on host tissue: molecular mode. Cancer Biol Med. 2017;14(3):254–70.
54. Chapuy B, Roemer M, Stewart C, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. Blood. 2016;127(7):869–81.
55. Davis RE, Ngo V, Lenz G, Tolar P, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature. 2010;463(7277):88–92.
56. Wilson WH, Young R, Schmitz R, Yang Y, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21(8):922–6.
57. Bernard S, Goldwirt L, Amorim S, Brice P, et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. Blood. 2015;126(14):1695–8.
58. Grommes C, Pastore A, Palaskas N, Tang SS, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma. Cancer Discov. 2017;7(9):1018–29.
59. Choquet S, Houillier C, Bijou F, Houot R, et al. Ibrutinib monotherapy in relapse or refractory Primary CNS Lymphoma (PCNSL) and Primary Vitreo-Retinal Lymphoma (PVRL). Result of the Interim Analysis of the iLOC Phase II Study from the Lysa and the French LOC Network. Blood. 2016;128(22):784.
60. Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell. 2017;31(6):833–43.
61. Grommes C, Younes A. Ibrutinib in PCNSL: the curious cases of clinical responses and aspergillosis. Cancer Cell. 2017;31(6):731–3.
62. Grommes C, Stone J, Nolan C, Tsyvkin E, Wolfe J, Mellinghoff IK, et al. Phase 1B of ibrutinib and high-dose methotrexate for recurrent/refractory CNS lymphoma. J Clin Oncol. 2017;35(15_suppl):7533.
63. Andorsky DJ, Yamada R, Said J, Pinkus GS, 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(13):4232–44.
64. Lesokhin AM, Ansell S, Armand P, Scott EC, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol. 2016;34(23):2698–704.

65. Rubenstein JL, Fridlyand J, Shen A, Aldape K, et al. Gene expression and angiotropism in primary CNS lymphoma. Blood. 2006;107(9):3716–23.
66. Nayak L, Iwamoto F, LaCasce A, Mukundan S, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood. 2017;129(23):3071–3.
67. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, Pileri SA, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer. 2011;117(22):5058–66.
68. Yang Y, Shaffer AI, Emre NC, Ceribelli M, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. Cancer Cell. 2012;21(6):723–37.
69. Wu L, Adams M, Carter T, Chen R, et al. Lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res. 2008;14(14):4650–7.
70. Wang M, Fowler N, Wagner-Bartak N, Feng L, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia. 2013;27(9):1902–9.
71. Zinzani PL, Pellegrini C, Gandolfi L, Stefoni V, et al. Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 2 trial. Clin Lymphoma Myeloma Leuk. 2011;11(6):462–6.
72. Rubenstein JL, Fraser E, Formaker P, Lee JCC, et al. Phase I investigation of lenalidomide plus rituximab and outcomes of lenalidomide maintenance in recurrent CNS lymphoma. J Clin Oncol. 2016;34(15 Suppl):7502.
73. Ghesquieres H, Houillier C, Chinot O, Choquet S, et al. Rituximab-Lenalidomide (REVRI) in relapse or refractory Primary Central Nervous System (PCNSL) or Vitreo Retinal Lymphoma (PVRL): results of a "Proof of Concept" phase II study of the French LOC Network. Blood. 2016;128(22):785.
74. Tun HW, Johnston P, Grommes C, Reeder CB, et al. Phase I clinical trial on pomalidomide and dexamethasone in treating patients with relapsed/refractory primary central nervous system lymphoma (PCNSL) or primary vitreoretinal lymphoma (PVRL). J Clin Oncol. 2017;35(15 Suppl):7516.
75. Kuhn JG, Chang S, Wen PY, et al. Pharmacokinetic and tumor distribution characteristics of temsirolimus in patients with recurrent malignant glioma. Clin Cancer Res. 2007;13(24):7401–6.
76. Korfel A, Schlegel U, Herrlinger U, Dreyling M, et al. Phase II trial of temsirolimus for relapsed/refractory primary CNS lymphoma. J Clin Oncol. 2016;34(15):1757–63.
77. Schuster SJ, Svoboda J, Chong EA, Nasta SD, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377(26):2545–54.
78. Neelapu SS, Locke F, Bartlett NL, Lekakis LJ, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–44.
79. Kochenderfer JN, Dudley M, Kassim SH, Somerville RP, 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.
80. Grupp SA, Kalos M, Barrett D, Aplenc R, et al. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368(16):1509–18.
81. Abramson JS, McGree B, Noyes S, Plummer S, et al. Anti-CD19 CAR T cells in CNS diffuse large-B-cell lymphoma. N Engl J Med. 2017;377(8):783–4.