Review Article

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

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

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

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare sub-type of diffuse large B-cell lymphoma (DLBCL) that is exclusively confined to the central nervous system (CNS), including brain/spinal tissue and/or leptomeninges and/or vitreo-retinal compartment (1,2). Although these tumor cells appear similar to systemic DLBCL by histopathology, our understanding of the lymphoma biology and neurotrophism seen in PCNSL is still evolving. For the vast majority of patients, high dose methotrexate (HD-MTX) based regimens with rituximab form the backbone of

Table 1 Summary of selected prospective clinical trials investigating activity in refractory/relapsed PCNSL

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

PCNSL, primary central nervous system lymphoma.

first line remission-induction therapy for newly diagnosed patients with PCNSL. Eligible patients are typically offered consolidation therapy to improve the remission quality and survival outcomes. Although excellent responses are typically achieved and long term survivors are frequently seen (3), by contrast to systemic DLBCL, the risk of relapse after first-line therapy does not plateau even for those patients with sustained complete response (CR) for over 10 years of follow up (4-6). Re-biopsy is often difficult and not routinely performed at disease relapse/progression. Thus, most available data is derived from tissue obtained at initial diagnosis, further limiting our understanding of the patho-biology in rrPCNSL. In the setting of rrPCNSL, the optimal salvage regimen for patients remains elusive. We summarize selected prospective trials in rrPCNSL in *Table 1*.

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

Relapsed *vs.* refractory PCNSL

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

disease (25,26).

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

Defining relapse or recurrence

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

Predicting the risk of relapse in PCNSL

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

However, an independent single institution (n=338) dataset from Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) concluded that age and performance status were the only variables independently associated with survival on multivariable analysis. In this study, recursive partitioning analysis (RPA) was used to create independent prognostic classes which were subsequently validated in three prospective PCNSL trial cohorts from the Radiation Therapy Oncology Group (RTOG) (32). The authors identified three distinct prognostic classes: class 1 (age <50 years), class 2 [age ≥50; Karnofsky performance score (KPS) ≥70] and class 3 (age ≥50; KPS <70) delineating significant differences in outcome with regard to both overall and failure-free survival. The simplicity and generalizability of the MSKCC scoring system is a potential advantage over the IELSG scoring system. However, there are very limited data about the validity of these scoring systems in the context of rrPCNSL. Notably, all existing prognostic models are based on clinical parameters measured at baseline; no robust

data are yet available on dynamic factors measured during therapy and/or based on clinical, pathobiological or imaging characteristics of PCNSL (33-36). Identifying those most at risk of being refractory or relapse in PCNSL is further complicated by different first line regimens being employed in routine clinical practice (33).

Clinical challenges in the relapse/refractory setting

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

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

Folate antimetabolites

Re-challenge with HD-MTX

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

Pemetrexed

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

require hospitalization, but low-dose dexamethasone, folate, and B12 supplementation is recommended (9). These findings suggest that pemetrexed may have some efficacy in rrPCNSL but would require further evaluation in prospective studies prior to being adopted in routine practice.

Non-methotrexate-based chemotherapy approaches

Alkylating agents

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

Other cytotoxic chemotherapies and their combinations

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

A retrospective study reported the feasibility and activity of a combination of rituximab, ifosfamide and etoposide (R-IE regimen) in a multicenter series of rrPCNSL patients ≤75 years old (52). Patients in CR, PR or SD after the fourth course of R-IE were referred to WBRT or to high-dose chemotherapy supported by autologous stem cell transplant (HDT-ASCT) if previously irradiated. This study reports an ORR of 44% in 22 consecutive patients treated, with CR rate of 37% and 2 yr PFS of 21%.

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

High dose chemotherapy followed by autologous stem cell transplantation

High dose chemotherapy (HDT) followed by ASCT is demonstrably effective and now widely employed as consolidation therapy for patients with newly diagnosed PCNSL and many modern upfront HD-MTX-based protocols are typically more intensive, and often include consolidation HDT-ASCT (1,25,26,53,54). For systemic DLBCL, HDT-ASCT is considered standard of care for eligible patients with relapsed/refractory disease who achieve remission with second-line multiagent chemotherapy (55). Two decades ago, early data emerged demonstrating the potential efficacy for patients with rrPCNSL. Based on promising retrospective data (56-58), a multicenter phase 2 study evaluating HDT with thiotepa, busulfan and cyclophosphamide (TBC) with ASCT demonstrated CR in 26 of the 27 patients evaluated. Of the 26 patients, 15 where chemosensitive and achieved an objective response (12 CR, 3 PR) to salvage HD cytarabine and etoposide while the remaining were chemorefractory (59). The median PFS was 11.6 months and 2-year PFS was 45% in the overall study population. Encouragingly, the median

OS was not reached after a median follow up of 36 months in the chemosensitive group, while the median OS was 18.3 months for the chemorefractory group. More recently, a German cooperative group study for ASCT-eligible patients with rrPCNSL evaluated remission induction therapy with rituximab, HD-AraC and thiotepa followed by HDT-ASCT consolidation with rituximab/carmustine/thiotepa conditioning in 39 patients. In this phase 2 study, 56% of patients achieved CR after ASCT with an encouraging 2-year PFS of 46%, after a median follow up of 45 months (60). Inclusion of thiotepa in the conditioning regimen appears to be key; independently associated with improved outcomes (61,62). Although younger patients are more likely to be considered for HDT-ASCT approaches, a multicenter retrospective study supports this approach in appropriately selected older patients with rrPCNSL (median age: 67 yrs, range: 65–77 yrs) (63). Taken together, the published data support the role of HDT-ASCT consolidation for sufficiently fit patients with rrPCNSL who respond to second-line chemoimmunotherapy. The role of allogeneic transplantation remains experimental in this setting, although small retrospective reports provide early indications of feasibility, including patients who have relapsed following previous HDT-ASCT (64-66).

Approaches to enhance drug delivery across the neurovascular unit

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

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

Novel vascular targeting agents

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

Targeted agents

Anti-CD20 agents

Rituximab, an anti-CD20 monoclonal antibody has been increasingly employed in PCNSL treatment protocols given the CD20+ DLBCL histology and the established efficacy of rituximab when combined with chemotherapy for systemic DLCBL. Although some investigators question its potential utility due to its large molecular weight, it should be recognized that the NVU is dynamic and is neither permanently closed nor open. Moreover, there are other influential factors including lipid solubility, plasma half-life and active transport mechanisms that impact drug delivery into the CNS. Pre-clinical data (74,75), together with data from retrospective clinical studies support the efficacy of single agent rituximab or in combination with other agents in PCNSL (8,10,76-83). The multicenter

phase 2 IELSG32 study investigated three different induction chemotherapy regimens in a randomized fashion (arm A: HD-MTX plus HD-AraC; arm B: same as arm A plus rituximab; arm C: same as arm B plus thiotepa) (1). These data confirmed that the combination of an alkylating agent (thiotepa), two antimetabolites (methotrexate and cytarabine), and rituximab significantly improves outcome in terms of response rates, PFS and OS, although this study did not demonstrate a statistical difference between arm A and B (HD-MTX plus HD-AraC *vs.* HD-MTX plus HD-AraC plus rituximab). By contrast, a randomized phase 3 study (HOVON 105/ALLG NHL 24) did not find a benefit for rituximab in the context of a different chemotherapy backbone, without HDT-ASCT consolidation (84). Subsequently, the trial-level data from the two randomized studies were pooled and analyzed as a meta-analysis (a total of 343 patients); Schmitt *et al.* conclude that rituximab in combination with MTX-based chemotherapy improves PFS in newly diagnosed PCNSL, but evidence for an OS benefit was not forthcoming from this analysis (85). In addition to rituximab's role in targeting CD20, emerging evidence suggests that it may also play an adjuvant immunomodulatory role (86,87).

Bruton's tyrosine kinase inhibitors

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

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

Mammalian target of rapamycin (mTOR) inhibitors

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

Immunomodulatory approaches

IMiDs

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

Immune check point inhibitors

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

Chimeric antigen receptor (CAR) T-cell therapy

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

Conclusion

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

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