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Primary Central Nervous System Lymphoma: Focus on Indian Perspective

Praful Pandey, Ahitagni Biswas, Saphalta Baghmar, Mukesh Patekar and Ranjit Kumar Sahoo

Abstract

Early suspicion, withholding steroids, stereotactic biopsy, and high-dose methotrexate (HD-MTX) are essential for the treatment of primary CNS lymphoma (PCNSL) making its management in lower-middle-income countries (LMIC) challenging. Novel radiological methods, clinician awareness about the disease, and utilization of drugs like thiotepa and ibrutinib which can be given on an outpatient basis may allow better management of these patients in resource-poor settings. Combined with a late presenting demographic, this results in poorer outcomes in the Indian subcontinent as compared to its western counterparts. In this review, we summarize the currently available data on PCNSL in the Indian subcontinent. We also review the current standard of care for PCNSL and present potential modifications or research areas that may potentially improve outcomes in LMIC.

Keywords: primary central nervous system lymphoma, PCNSL, lower middle income countries, LMIC, methotrexate, TEDDI, ibrutinib

1. Introduction

WHO 2016 classification for lymphomas [1] defines primary central nervous system lymphoma as a rare and aggressive form of extranodal diffuse large B-cell lymphoma (DLBCL) involving the brain, leptomeninges, or eyes without any systemic involvement. However, this entity responded poorly to conventional DLBCL regimens [2, 3] despite using radiotherapy or dexamethasone to enhance CNS efficacy. Further evidence supporting PCNSL as a distinct entity comes from studies showing unique GEP signatures [4] and transcriptomics (with heavy reliance on NF- κ B) [5] compared to its nodal counterparts.

PCNSL is predominantly a disease of the elderly [6] and presents with focal deficits followed by features of raised intracranial pressure [7]. Initially suspected on MRI, it is typically diagnosed by a stereotactic biopsy or by cerebrospinal fluid evaluation in exceptional circumstances [8]. Modern management is based on HD-MTX based polychemotherapy followed by consolidative therapy in the form of WBRT, standard-dose chemotherapy or high-dose chemotherapy followed by stem cell transplantation. Rituximab addition may improve outcomes [9]. Novel ibrutinib-based combinations are used in relapsed settings and are being evaluated in the frontline settings as well [10].

In the LMIC, the lack of availability of HD-MTX and neurosurgical suites make management of PCNSL difficult. Novel MRI-based sequences, ibrutinib-based regimes, and utilization of consolidative WBRT may ease the burden. This review details the epidemiological, clinical, and radiological features of PCNSL with a focus on the Indian subcontinent. Furthermore, the current standard of therapy and potential modifications for easier delivery in the LMIC is also detailed.

2. Epidemiology

2.1 Incidence

Overall, the age-adjusted incidence rate (SEER database) of PCNSL is .47 cases per 10,000,000 people per year [11].

The incidence is increasing in elderly males for unclear reasons. Variations in CD4 subpopulations could be a likely cause [12].

From India, only two studies have reported temporal incidence trends. One study reported a 3.5× increase in the number of cases without any change in the proportion of all CNS neoplasms from 1980 to 2003 [13]. Another study done at a single center in northern India found no temporal variation in incidence [14].

2.2 Place in the lymphoma landscape

PCNSL accounts for 4% of all primary CNS tumors as per western data [15]. Two Indian studies, however, report a more conservative estimate of 0.92–0.95% [13] and 1.2% [14].

PCNSL is an uncommon NHL accounting for 4–6% of all extranodal lymphomas [11] and less than 1% of all NHLs as per western literature. A study from Southern India reports that PCNSL accounts for 9.6% of all primary extranodal lymphomas and roughly 3% of all NHLs [16].

2.3 Demographics

Table 1 contains the demographic details of PCNSL patients recruited in Indian studies.

In Western settings, non-HIV infected PCNSL is typically diagnosed at 45–65 years of age (median age of diagnosis in the fifth decade) with no gender predilection [6, 17–19]. However, the Indian demographic differs in having a younger affected population (median age at diagnosis ranging from 42 to 59 years) with slight male preponderance [13, 14, 20–31]. These changes are more likely from different population demographics rather than inherent disease biology, given that individuals aged more than 60 or 65 consistently amount to less than 9% and 7% of the total Indian population respectively [32].

HIV-infected individuals are also a younger cohort (Median age: 37 years) with a male preponderance [12].

Among transplant recipients: CNS involvement is present in 15% of all NHL cases [33] and is associated with a poorer prognosis [34]. However, amounting to only 0.9% of all PCNSL cases, this subset is not well studied [12].

2.4 Global vs. Indian burden of HIV in PCNSL

The prevalence of HIV in PCNSL patients is estimated to be 6.1% globally, with significant variation among nations [35]. Prevalence in India is significantly lesser

Study (n)	Demographics			Clinical presentation						Investigations			
	Median age (years)	Males (%)	HIV positive (%)	Median duration of symptoms (Months)	Most common presenting feature	Eye involvement (%)	Leptomeningeal involvement (%)	ECOG PS	Raised LDH (%)	Histopathology	Stereotactic biopsy (%)	Inadvertent resection (%)	Multiple lesions (%)
Patekar et al. (n = 99)	50	65.60	1.10	3.5	Neurological deficit	19.40	15.8	58.5% PS $\geq$ 3	19.40	DLBCL (97.7%)	49	40	81.80
Adhikari et al. (n = 22)	51.5	59	0	4	Neurological deficit	22.70	13.64	59.9% PS $\geq$ 3	45.45	DLBCL (100%)	50	50	75
Patel et al. (n = 73)	46	66	0	2.5	Raised ICP	—	—	—	—	DLBCL (95.9%)	54.80	45.20	64.40
Powari et al. (n = 40)	50	66	0	—	Raised ICP	—	—	—	—	DLBCL (100%)	—	100	87.50
Paul et al. (n = 56)	42	60	0.90	—	Raised ICP	—	—	—	—	DLBCL (93.2%)	—	—	21.40
Mahadevan et al. (n = 24)	53	58.33	0	—	Raised ICP	—	—	—	—	DLBCL (100%)	—	—	—
Dash et al. (n = 41)	52	53.40	0	—	Raised ICP	—	—	—	—	DLBCL (100%)	—	—	—
Sarkar et al. (n = 116)	44.4	69.30	0.80	—	—	—	—	—	—	DLBCL (100%)	—	—	—
Parischa et al. (n = 66)	46	50	0	—	Raised ICP	—	—	—	—	DLBCL (100%)	—	—	15
Sharma et al. (n = 65)	49	58.30	0	—	—	—	3	—	—	DLBCL (100%)	—	—	41.53

Study (n)	Demographics			Clinical presentation						Investigations			
	Median age (years)	Males (%)	HIV positive (%)	Median duration of symptoms (Months)	Most common presenting feature	Eye involvement (%)	Leptomeningeal involvement (%)	ECOG PS	Raised LDH (%)	Histopathology	Stereotactic biopsy (%)	Inadvertent resection (%)	Multiple lesions (%)
Yadav et al. (n = 32)	50	71	0	—	Raised ICP	0	0	—	—	DLBCL (100%)	—	—	68.80
Rudresha et al. (n = 26)	42.5	65.30		—	Raised ICP	0	4	—	30.70	DLBCL (96%)	46	54	38.50
Rudresha et al. (n = 53)	44	64	3.70	—	Raised ICP	0	6	—	32	DLBCL (100%)	49	51	30
Kumari et al. (n = 30)	47.8	60	0	—	Raised ICP	—	—	70% with PS $\geq$ 3	70	DLBCL (100%)	—	—	66
Puligundla et al. (n = 42)	46	68.70	4.70	—	Raised ICP	0	15.80	80.9% PS $\geq$ 2	—	DLBCL (97.6%)	42.80	57.10	23.80
Agarwal et al. (n = 26)	59	61.50	7.60	3	Neurological deficit	—	19.20	—	34.60	DLBCL (96.1%)	—	—	77

Table 1.
Demographic and clinical details of patients enrolled in Indian studies.

[35], with some studies not reporting even a single case [14, 25–27, 30]. Similarly, PCNSL accounts for 2.5% of all CNS lesions in HIV-positive patients compared to 10–17% in the western population [36]. Autopsy series show similar findings with the only published Indian series reporting no cases of PCNSL over 8 years [37] while western studies report the share to be between 1.4 and 3% [38, 39]. Shorter survival among AIDS patients in the Indian subcontinent could be the likely cause [40].

3. Clinical features and diagnosis

3.1 Presenting features

The most common presenting features reported are focal neurological deficits, neuropsychiatric symptoms, headache from raised intracranial pressure (ICP), seizures, and ocular symptoms [7]. Diagnosis may not be evident at presentation, with one study reporting a median time lag of 70 days from symptom onset to neuroimaging [41]. Personality changes and visual hallucinations are usually detected late, and a lower threshold to pursue neuroimaging is needed [41].

3.2 Clinical evaluation

Any suspected case of PCNSL should undergo neuroimaging in the form of a contrast-enhanced MRI of the brain and spine, CSF analysis unless contraindicated (ideally before stereotactic biopsy), slit-lamp examination, and testicular examination (in males) [42].

In some cases, pathological evaluation of ocular material or CSF may diagnose. In most cases, however, a stereotactic biopsy is needed [43]. The stark difference in the initial management of PCNSL, compared to high-grade gliomas, underlines the importance of early clinical suspicion and radiological expertise.

3.3 The Indian scenario

Table 1 contains the clinical features of patients enrolled in studies in Indian settings.

In the Indian subcontinent, delayed health-seeking behavior combined with high initial misdiagnosis rates leads to a high disease burden at presentation. Median time from symptom onset to diagnosis is reported around 3.5–5 months in Indian studies [20, 24, 29, 44], compared to 2.5–3 months in western studies [7, 41].

Delayed health-seeking behavior is evident if we compare clinicoradiological features at index presentation. While two studies report focal neurological deficits as the most common presenting feature [20, 29], most studies report headache from raised ICP as the index presentation [14, 21–23, 27, 28, 30, 31], which is typically a late feature in the western literature. Furthermore, while most western patients are ambulatory and capable of self-care at presentation [7], roughly 2/3rd of Indian patients are ECOG performance status (ECOG-PS) three or worse in retrospective [22, 25, 29] and prospective [44] studies. Similarly, multifocal lesions, reported in 25% of patients at presentation as per western literature [7], are seen in 30–82% of all patients presenting in the Indian settings [20, 22, 24–29, 31, 44]. However, some studies do give estimates nearing their western counterparts [14, 23, 30], perhaps highlighting differential health-seeking behavior.

Erroneous evaluation and emergent management are also common. Indian studies report misdiagnosis rates as high as 54% [20] to 100% [29], and inadvertent open surgical resection in 36–57% [20, 44] of PCNSL patients compared to 25% in

western literature. In addition, inadvertent steroids are given before diagnosis in up to 2/3rd patients referred from primary care [20] although prospective studies document only 9% requiring corticosteroid therapy for life-threatening indications [44].

These delays and errors result in a patient population with advanced disease and a poorer prognosis. While the proportion of patients with LDH elevation (1/3rd) and CSF Protein elevation (2/3rd) are similar in Indian [22, 25, 28, 29, 31] and western studies [45], fewer patients are IESLG low risk in the Indian settings with concomitant better outcomes [22, 25, 29]. However, the MSKCC risk classification seems to underestimate the risk in the Indian population because of its weightage to older age [28, 31].

4. Treatment modalities and outcomes

Table 2 shows treatment details and outcomes of important studies from the Indian subcontinent.

4.1 Survival outcomes

4.1.1 Evolution of treatment modalities

Left untreated, PCNSL has a uniformly dismal prognosis (median OS = 2 months) [46]. Only marginally better are conventional DLBCL regimes with response rates ranging from 19 to 59% and less than half patients surviving at two years from diagnosis [2, 3]. A significant improvement in prognosis comes from modern multi-drug regimens incorporating high-dose methotrexate (HD-MTX) with appropriate consolidation (2 years OS of 80% and a five-year OS of 77%) [47]. More recent regimes utilizing autologous stem cell transplantation as consolidation report two-year OS as high as 81% [48].

4.1.2 Outcomes reported in India

Indian studies report modest outcomes. Up to 20% of PCNSL patients never receive therapy [20, 22, 29]. A single-institution reported a median EFS of 20.4 months and a median OS of 31.7 months at a median follow-up of 34 months with HD-MTX-based multiagent regimes and Rituximab and consolidative WBRT. [20] A prospective phase 2 trial evaluating response adapted radiotherapy showed a median OS of 19 months, underlining the necessity of consolidative WBRT to optimize outcomes [44]. A study evaluating the importance of HD-MTX therapy in the Indian setting [28] reported a median OS of 8 months, 13 months, and 23 months in WBRT, R-CHOP with WBRT, and HD-MTX with WBRT, respectively. Thus, there is a scope for improvement in the outcomes of PCNSL seen in the Indian sub-continent.

4.2 Long term toxicity

Studies using HD-MTX-based induction and WBRT consolidation report 15% long-term neurotoxicity rates [49]. However, no such delayed sequelae are documented in prospective studies using abbreviated WBRT [50, 51]. On the other hand, regimes using ASCT as consolidation report continuous cognitive improvement until 12–18 months after completion of therapy [48].

Study (n)	Pre-treatment details		Induction chemotherapy details				Post-induction chemotherapy	Long-term outcomes			
	IESLG low risk (%)	Treatment received (%)	Type of chemotherapy	Median induction cycles	Rituximab	Overall response rate, complete response rate (ORR/ CR %)		Median follow-up duration (months)	Median event-free survival (months)	Median overall survival (months)	Severe late neurotoxicity (%)
Patekar et al. (n = 99)	7.10	77.70	MVP with Rituximab (94.8%) CHOP + HTMTX (2.6%) CHOP + IT MTX (1.3%) HD - MTX only (1.3%)	5	In affording patients	81.8% (46.8%)	WBRT in 54% (Ara - C in 86% of WBRT recipients) 11% HiDAC only	34	20.4	31.7	10
Adhikari et al. (n = 22)	—	100	MVP	5	In affording patients	93.7% (52.63%)	50% WBRT 50% reduced dose WBRT 68.18% post-WBRT HiDAC	11.25	Not reached	19	—
Parischa et al. (n = 66)	—	100	MPV followed by WBRT + HiDAC (DeAngelis protocol)	—	No	—	—	—	—	—	—
Yadav et al. (n = 32)	—	100	WBRT (36-50 Gy) followed by 6 cycles CHOP	6	No	87.5% (75%)	None	18	—	14 months	—
Rudresha et al. (n = 26)	—	100	DeAngelis protocol (92%), MTR followed by EA (8%)	5	No	ORR for DeAngelis: 92%, ORR for MTR regime: 100%	WBRT followed by HiDAC given in DeAngelis protocol, EA given to MTR recipients	—	—	20.5	—

Study (n)	Pre-treatment details		Induction chemotherapy details			Post-induction chemotherapy		Long-term outcomes			
	IESLG low risk (%)	Treatment received (%)	Type of chemotherapy	Median induction cycles	Rituximab	Overall response rate, complete response rate (ORR/ CR %)		Median follow-up duration (months)	Median event-free survival (months)	Median overall survival (months)	Severe late neurotoxicity (%)
Rudresha et al. (n = 53)	—	100	DeAngelis protocol (n = 31) CHOP + WBRT (n = 14) WBRT only (n = 6)	—	No	—	WBRT followed by HiDAC in DeAngelis protocol	—	—	23 months for DeAngelis protocol, 13 months for standard CHOP + WBRT treated, 6 months for WBRT only subset	26% in DeAngelis treated, 14% in CHOP + WBRT subset
Kumari et al. (n = 30)	10	100	40–52 Gy WBRT followed by 6 cycles of CHOP/PCV	—	No	—	—	—	—	—	—
Puligundla et al. (n = 42)	19	80.90	Modified DeAngelis (50%) Modified DeAngelis protocol + rituximab (29.4%) Steroids + radiotherapy (17.7%) BFM- NHL protocol (3%)	—	Given to 29.4% of patients	—	—	18	11	15.9	—
Agarwal et al. (n = 26)	36.3	84.60	MVP + Cytarabine	—	No	CR: 72.7%	WBRT in patients aged < 60 years (45%)	14.5	—	10	31.25%

Table 2.
Treatment administered and long term prognosis of PCNSL patients enrolled in Indian studies.

In the Indian setting, reliable estimates of long-term neurological toxicity are lacking given that most of the reported literature does not have adequate follow-up or assessment [22, 25–27, 30, 31]. However, limited studies report severe long-term neurotoxicity rates of 10–33%, with elderly patients and WBRT recipients at a higher risk [20, 28, 29].

5. How can we improve?

PCNSL requires multi-disciplinary care in resource-intense settings to optimize outcomes. However, in lower-middle-income countries (LMIC), the main barriers to applying modern evidence-based management of PCNSL are the lack of neurosurgical facilities and oncology units capable of handling HD-MTX.

5.1 Improving diagnosis

5.1.1 Better radiological support

Radiological differential diagnosis of PCNSL includes high-grade gliomas, tumefactive demyelinating lesions, metastasis, and granulomatous diseases/infections. Although, the radiological appearance of PCNSL is very distinctive with homogenous contrast enhancement, optic pathway, and cranial nerve infiltration, a predilection for deeper structures, lesser necrosis, and nearly no bleeding, many studies still report diagnostic difficulties while using conventional MRI only [52]. This differentiation is crucial because while PCNSL requires stereotactic biopsy followed by systemic chemotherapy, high-grade gliomas are usually treated with upfront gross total resection. With 40% of patients responding, prior steroid usage compounds this problem with high false-negative biopsy rates [53]. Thus, early radiological suspicion may allow many patients to undergo appropriate management in the form of no inadvertent steroid therapy, stereotactic biopsy, and early institution of HD-MTX-based therapy.

5.1.2 Conventional MRI sequences

Diffusion-weighted imaging is an essential diagnostic tool. PCNSL shows more restricted ADC than high-grade gliomas, given its higher cellular density and N:C ratio. However, solid portions of high-grade gliomas may mimic [52]. Therefore, a different measure, “Relative minimum ADC,” is often used given its reasonable diagnostic certainty [54]. Furthermore, dynamic contrast-enhanced MRI adds to ADC’s diagnostic performance as well [55].

Another crucial diagnostic aid is the ^1H -magnetic resonance spectroscopy (^1H -MRS). Choline to creatine ratio, a marker of membrane turnover, is identical for PCNSL and high-grade gliomas. However, N-acetyl aspartate peaks (NAA), a marker of neuronal damage, may have variable results. The lipid peak arises from necrosis in GBM and release of fatty moieties via lymphocytes in PCNSL, making lipid resonance without necrosis the most specific finding [56].

^1H -MRS may allow assessment of other peaks as well. Conventional 1.5 T MRI cannot differentially assess glutamate (Glu) and glutamine (Gln) peaks, and there is no difference in Glutamate + Glutamine/ Creatinine peaks among PCNSL and high-grade gliomas. However, because of impaired Glutamate internalization in high-grade gliomas, glutamate to glutamine conversion is upscaled. Thus, 3 Tesla MRI machines which can differentially quantify glutamate and glutamine, allow

assessment of Glu/Glu + Gln ratios which are reproducibly different in PCNSL and high-grade gliomas [57].

5.1.3 Newer MRI based modalities

Amide proton transfer weighted studies (based on 3 T MRI machines) also detect endogenous mobile proteins and peptides predominantly seen in the cytoplasm. PCNSL, with its high N:C ratio and thus, a low concentration of mobile proteins, shows much less limited hyperintensities as compared to heterogeneous hyperintensities much larger than the gadolinium-enhancing areas in high grade gliomas [55].

Dynamic susceptibility contrast-enhanced MRI can differentiate based on different tumor microenvironments. PCNSL lacks florid neovascularization compared to high-grade gliomas, as assessed by FVIII staining on resected specimens [58]. Contrast enhancement stems from breakage of the blood-brain barrier rather than increased vascularity resulting in a relatively lower rCBV than high-grade gliomas [59]. Neovascularization of surrounding infiltrated tissue can result in a specific shoulder-like pattern of signal intensity and enhance diagnostic performance [60]. Prospectively validated studies report an rCBV threshold of 2.56 having >90% sensitivity and specificity [54].

5.1.4 Machine learning: better analysis of conventional MRI meta-data

Fundamental differences of neovascularization and necrosis between PCNSL and high-grade gliomas may lead to subtle differences in imaging, which, although may not be evident to the human eye, are picked by metadata-based machine learning (ML) models. A recent meta-analysis assessing the utility of ML models for PCNSL diagnosis reports 0.878 as the lowest AUC across eight studies [61]. Another prospectively validated model reported an AUC of 0.978 using only T1 weighted images [62]. ML-based algorithms have advantages of being open access, easily accessible, and minimal reliance on novel machines or software. However, overfitting of models compromising external validity and prompting institute-specific algorithms is a challenge.

5.1.5 Metabolic imaging

Given its high cellular density, PCNSL shows intense homogeneous FDG uptake (as opposed to heterogeneous uptake in high-grade gliomas) with SUVmax values around 12–14 (2.5 times of normal gray matter). However, surrounding physiological gray matter uptake hinders accurate assessment [63]. A study assessing the diagnostic utility of PET/CT for PCNSL reported an optimal SUVmax cut-off of 15 with only a single false positive [64]. Another study reported that a SUVmax cut-off of 12 had 86% accuracy as a standalone modality and 95% when combined with CE-MRI with DWI [65].

The tumor/normal (T/N) ratio overcomes the reliance of SUVmax on plasma glucose concentrations. A study reported good diagnostic performance with a cut-off 2.0. Prior Steroids may hinder both SUVmax, as well as T/N ratio [66]. PET/CT has additional utility in ruling out secondary CNS lymphoma and a 7% additional yield over CT and bone marrow examination [67].

5.2 Cerebrospinal fluid analysis

CSF analysis may allow diagnosis without neurosurgical procedures and its associated complications in up to 40% of patients. Therefore, patients without

evidence of raised ICP should undergo CSF analysis with cytomorphology, flow-cytometry, and PCR for IGHV rearrangements either before or at least 1 week after the stereotactic biopsy [42].

A recent systematic review of 27 studies evaluating CSF cytomorphology and flow cytometry across different lymphoid neoplasms with meningeal involvement reported around 0.3-42.9% positive results with dual testing. Furthermore, 48% and 89% of studies reported samples positive on cytomorphology or flow cytometry alone, respectively, highlighting the importance of co-testing [68]. Another study assessing only PCNSL patients reported 13.3% and 23.3% positivity rates with CSF cytomorphology and flow cytometry, respectively [69].

CSF cell fragility impairs the diagnostic performance of cytomorphology and flow cytometry. However, PCR-based analysis of IGHV rearrangements to assess clonality does not require intact cells and may circumvent this problem. A study assessing IGHV rearrangement status in CSF among patients with PCNSL reported a sensitivity of 54% and specificity of 97% among the 84% patients having CSF with extractable DNA. The positive predictive value was 93%, with a further rise if only therapy naïve patients were considered [70]. However, a study prospectively evaluating CSF of 282 patients with PCNSL reported 10% samples with positive IGHV rearrangement PCR but negative cytomorphology and 12% samples with positive cytomorphology but negative IGHV rearrangement analysis [71]. Thus, IGHV rearrangement analysis may be better suited as an add-on than a replacement.

Novel approaches such as digital droplet PCR (ddPCR) analysis of MYD88 mutations [72], IL-10 levels [73], Osteopontin levels [74], neopterin levels [75], and miR-21 levels [76] may allow further diagnostic aid and potential negation of neurosurgical procedures in the future. Specifically, a meta-analysis reported that CSF IL-10 levels have a sensitivity of 81%, specificity of 97%, and an area under ROC of 0.95 at a cut-off of 6.88 pg/ml [77].

5.2.1 Slit lamp and intra-ocular biopsy

Like CSF analysis, Ocular involvement may also allow early diagnosis without reliance on neurosurgical procedures. Ocular involvement is seen in 15-25% of PCNSL patients, and slit-lamp examination is the diagnostic procedure of choice [78]. If involvement is suspected, a biopsy of vitreous fluid, choroid, or retina may allow histopathological diagnosis. Routine use of slit-lamp microscopy and a high index of suspicion is warranted given that more than 1/3rd of patients with ocular involvement are asymptomatic [79]. In cases with equivocal appearances, ocular ultrasound, fundus fluorescein angiography, and optical coherence tomography are adjunctive studies used for diagnosis [80].

Combined cytopathology, flow cytometry, and analysis of IGHV gene arrangement studies on multiple vitrectomy specimens have a combined sensitivity and specificity of 64% and 100%, respectively [81]. A chorioretinal biopsy is an option in suspicious cases with a normal vitreous biopsy [82].

Novel techniques may enhance diagnostic yields. For example, ARMS PCR-based MYD88 L265P mutation analysis is diagnostic in 86.7% FFPE samples of primary vitreoretinal lymphoma [83]. Techniques independent of DNA input such as ddPCR allow similar rates of MYD88 mutation detection from less invasive specimens like aqueous humor [72]. Lastly, elevated IL-10 levels or an IL-10/IL-6 ratio > 1 is suggestive but not diagnostic, and its utility as a standalone modality requires validation [78].

5.3 Improving therapy

5.3.1 Non-methotrexate containing induction regimes

High-dose methotrexate-based multiagent chemotherapy followed by consolidation with WBRT or autologous stem cell transplantation is the modern standard of care for PCNSL [42]. However, centers with facilities and experience for HD-MTX are lacking, necessitating the evaluation of alternative regime backbones.

Methotrexate doses of more than 3 g/m^2 are needed to cross the BBB and doses as high as 8 g/m^2 have been used without any guiding prospective randomized data. A recent observational study has reported higher CR rates and PFS with higher dose HD-MTX (8 g/m^2) [84]. An infusion time of 3 hours and 6 hours for doses of 3 g/m^2 and 8 g/m^2 respectively allows better CNS penetration per unit dose, allowing enhanced efficacy and an attenuated toxicity profile [85]. 5–7 cycles of HD-MTX-based polychemotherapy spaced at 2 weeks intervals rather than 3-week intervals are associated with optimal oncological outcomes [86]. Leucovorin rescue is typically started 24 h after infusion and at least 12 doses are given at 6-hour intervals [51]. The utility of therapeutic drug monitoring remains to be proven in these settings with a recommendation for assessment at 24 h, 48 h, and 72 h after initial infusion [87].

Thiotepa, a lipid-soluble organophosphorus-derived alkylator, is a potential answer. Evidence suggests that Methotrexate is optimally given in doses more than 3.5 g/m^2 over shorter infusion times (3 h) at a gap of 2–3 weeks for 5–8 cycles [42]. High dose cytarabine (Ara-C) addition to HD-MTX therapy led to more than doubling of responses, likely from prolonged exposure to S-phase cytostatics [88]. Subsequently, the IESLG32 study evaluated Rituximab addition and autologous SCT's utility in PCNSL and added Thiotepa to a third induction arm (MATRIx regime), which outperformed both combination chemotherapy and chemoimmunotherapy arms [9]. Thus, with a 100% plasma-to-cerebrospinal fluid ratio, 30-min infusion time, and synergy with anti-metabolites, Thiotepa might be a convenient alternative to HD-MTX, and the comparative efficacy of Thiotepa-high-dose Ara-C vs. HD-MTX is worth exploring. Notably, a study using high dose Ara-C with Thiotepa after initial HD-MTX showed an increase in responses [89].

Single-agent temozolomide [90], topotecan [91], and temsirolimus [92] have also shown modest activity in relapsed PCNSL settings, and different combinations may be worth evaluating.

Frequent mutations in the BCR subunit CD79B and Toll-like receptor adaptor protein MYD88 suggest addiction of PCNSL to BCR signaling [93], making Ibrutinib an attractive option. However, since Ibrutinib-driven responses in ABC DLBCL last for less than a year [94], cotherapy with blood-brain barrier crossing synergistic drugs is prudent. Recent studies have built on this, and Ibrutinib-based combination regimes are a promising HD-MTX-free approach. While Ibrutinib is antagonistic with most anti-folate drugs, it is synergistic with etoposide, doxorubicin, Ara-C, and mitomycin C [95]. Additionally, doxorubicin, a broad spectrum lymphocytic but BBB impermeable agent, may be given as a liposomal formulation that maintains CSF concentrations throughout therapy duration, likely from a reservoir-like effect [96]. On these lines, the dose-adjusted TEDDi-R regime given after a 14-day run-in of ibrutinib monotherapy showed 86% complete responses in a phase 1b study with 18 patients [97]. Notably, the activity of this regime did not become dependent on the presence of the specific MYD88 L265P mutation. However, severe adverse effects in the form of grade 4 neutropenia, grade 4 thrombocytopenia, and invasive fungal infections (most commonly aspergillosis) were noted in 53%, 30%, and 50%, respectively. These rates of invasive fungal infections

are not found in other studies evaluating Ibrutinib (with or without steroids), and monocyte BTK inhibition may be causative [98]. Recognizing the need for prophylaxis, a recent phase 1b trial reported 75% CR rates and no invasive fungal infections with DA-TEDDi R with Isavuconazole prophylaxis [95]. In the Indian settings, concomitant dose reduction of both ibrutinib and liposomal doxorubicin [99] makes Voriconazole prophylaxis an attractive option offering maintained efficacy and reduced financial toxicity.

Lenalidomide may offer a potentially less intensive ibrutinib-based option. Given its capability to expand NK-cell pools, Lenalidomide is known to be synergistic with Rituximab (R^2 -regimen) [100]. A proof-of-concept phase 2 study documented ORR and CR rates of 32% and 29%, respectively, in relapsed/refractory PCNSL with a tolerable safety profile [101]. Building on data from systemic DLBCL, ibrutinib and R^2 (IR^2) leads to complete responses in 1/3rd relapsed/ refractory PCNSL cases, and studies testing this regime in frontline settings are eagerly awaited [10].

Intrathecal delivery may enhance synergy between rituximab and lenalidomide. At conventional doses (375 mg/m^2), CSF compartment achieves only 0.1% of systemic rituximab concentrations [102]. Evidence suggesting that incorporation of systemic rituximab in lymphoma protocols does not impact the incidence of CNS relapse also points to potential inadequacy of intravenous rituximab in clearing the leptomeningeal compartment [103]. Given the acceptable safety profile of intrathecal rituximab in non-human primates [104], intrathecal rituximab-based combinations deserve consideration for further research. On these lines, a phase 1 study reported 25 mg as the optimal intraventricular dose (via ommaya reservoir) leading to an ORR of 60% and a CR rate of 40% with one parenchymal remission as well [105]. A subsequent study reported a CR rate of 43% in relapsed PCNSL when treated with a combination of intraventricular rituximab and methotrexate [106]. Thus, while intraventricular rituximab is an option with promising efficacy and cost benefits, larger studies are needed. Additionally, the utility of intrathecal rather than intraventricular therapy also requires consideration.

5.3.2 Optimizing consolidation therapy

More than 50% of PCNSL patients relapse within 5 years of therapy if treated with induction alone, necessitating some form of consolidation therapy [107]. The two largest comparative trials indicate comparable efficacy but lesser long-term neurotoxicity with HDT-ASCT than WBRT [108, 109]. While a longer follow-up may tell a different story [50], upfront HDT-ASCT for all PCNSL patients is not feasible for resource-limited settings.

In Indian settings, WBRT followed by HiDAC [107] remains the most common consolidation therapy. However, while western studies report comparable efficacy and lesser neurotoxicity by reduced dose WBRT [51, 110], studies in the Indian settings in our experience are less favourable [44].

Non-myeloablative chemotherapy may offer a balance of efficacy and cognition. For example, Etoposide-Cytarabine (EA regimen) showed efficacy comparable to historic WBRT treated cohorts in a single-arm phase 2 study. However, lack of randomized comparisons and high rates of grade ≥ 4 hematological toxicity with the possible requirement of autologous stem-cell rescue are barriers to frequent utilization [111].

Maintenance with oral procarbazine, assessed in a phase 2 trial of elderly PCNSL patients, is a safe alternative, although randomized evidence is lacking [112]. Another study showed lesser relapse rates (non-randomized) with oral Temozolomide maintenance than WBRT, although atypical induction protocols

used in this study negatively impact the external validity of findings [113]. Lenalidomide maintenance is also a safe option in elderly patients, although the efficacy in this setting is yet to be proven [114].

6. Conclusion

PCNSL, although morphologically like any other DLBCL, has distinct pathobiology and prognosis. The requirement of early radiological diagnosis and referral to a center equipped with neurosurgical facilities and safe administration of HD-MTX for every patient makes management of PCNSL challenging in resource-limited settings. Non-invasive methods of diagnosis and non-HD-MTX-based therapies need more research to allow PCNSL cases to be managed optimally in such settings.

Author details

Praful Pandey¹, Ahitagni Biswas², Saphalta Baghmar³, Mukesh Patekar⁴ and Ranjit Kumar Sahoo^{1*}

¹ Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

² Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India

³ Department of Medical Oncology, Max Vaishali and Noida, India

⁴ Department of Medical Oncology, Fortis Memorial Research Institute, Haryana, India

*Address all correspondence to: drranjitmd@gmail.com

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