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doi.org/10.58931/cht.2025.4274

Management of Newly Diagnosed Primary Central Nervous System Lymphoma

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Introduction

The last decade has witnessed significant progress in the clinical management of patients with newly diagnosed primary central nervous system (CNS) diffuse large B-cell lymphoma (PCNS-DLBCL, hereafter referred to as PCNSL). Data from several clinical trials have demonstrated the potential for long-term remission in a proportion of patients, particularly those eligible for intensive multi-agent chemotherapy approaches.[1-3] High-dose methotrexate (HD-MTX)-based induction regimens remain standard-of-care globally for both younger and older patients with newly diagnosed PCNSL. However, with clinical trial data demonstrating the efficacy of multiple regimens (differing in partner chemotherapy agents, hematological toxicity, and MTX dose density), but with few randomized comparisons, the optimal induction regimen remains unclear.

Consolidation therapy is key to survival outcomes in PCNSL. Thiotepa-based autologous stem cell transplantation (TT-ASCT) has been widely adopted as the consolidation therapy of choice for patients ≤70 years. However, it is increasingly recognized that appropriately selected patients older than 70 years can also benefit from TT-ASCT consolidation.[4,5] In parallel, declining rates of whole-brain radiotherapy (WBRT) have been observed due to significant risk of neurotoxicity, particularly in patients aged ≥60 years.

This review summarises the contemporary clinical management of patients with newly diagnosed PCNSL. We focus on key diagnostic considerations, the landscape of evidence-based first-line treatments, and practical guidance for treatment selection and delivery. We also briefly discuss specific scenarios, including human immunodeficiency virus (HIV)-associated PCNSL and vitreoretinal involvement in the context of PCNSL.

Diagnosis and Staging

PCNSL, defined as large B-cell lymphoma (LBCL) arising from the parenchyma of the brain or spinal cord or leptomeninges, represents up to 4% of all brain cancers.[6] Patients with a suspected diagnosis of PCNSL should undergo whole-brain magnetic resonance imaging (MRI) with contrast, which typically reveals solitary (65%) or multifocal (35%) gadolinium-enhancing parenchymal lesions. Exclusive leptomeningeal involvement is rare. An early imaging review by an expert in neuroradiology is recommended. All efforts should be made to avoid corticosteroid use prior to biopsy due to an increased risk of a non-diagnostic sample.[7] Surgical resection does not improve outcomes, and less-invasive image-guided stereotactic approaches are therefore recommended.[6] Confirmation of diagnosis should involve a specialist hematopathologist review of tumour tissue. Typical histopathologic findings are a non-germinal centre LBCL phenotype; CD10 and Epstein-Barr virus (EBV)-positivity are uncommon and should prompt consideration for systemic lymphoma and immunodeficiency-associated lymphoma, respectively.[8] A minority of cases are diagnosed based on cytology supported by flow cytometry of cerebrospinal fluid (CSF).[7]

All patients should undergo body computed tomography (CT) or positron emission tomography (PET)/CT to exclude systemic lymphoma. An MRI of the spine is indicated for patients with relevant clinical symptoms or signs. Bone marrow biopsy (BMB) is not routinely recommended

for patients with a normal pattern of systemic fluorodeoxyglucose (FDG)-uptake on PET/CT.[6] BMB may also be considered if the clinical context suggests the possibility of underlying indolent lymphoma (e.g., presence of a paraprotein, cytopenias, or CD10-positive disease). It is good practice to also perform testicular ultrasound given the uncertain sensitivity of PET/CT for excluding testicular disease.

Expert ophthalmologic examination is recommended in all cases to exclude vitreoretinal lymphoma (VRL), which is present in up to 15% of PCNSL and is often asymptomatic.[9] In the context of biopsy-confirmed PCNSL, vitreous sampling or vitrectomy is not required to confirm VRL.

Where possible, CSF samples should be analyzed for cell count, protein levels, cytology, and flow cytometry. CSF abnormalities portend a poorer prognosis, and if CSF involvement is confirmed on cytology/flow cytometry, repeat sampling is required for response assessment.

Treatment of Newly Diagnosed PCNSL

General Considerations

Rituximab and HD-MTX-based regimens are standard-of-care for remission induction and are deliverable in the majority of patients, including those ≥60 years.[1,10,11] HD-MTX-based regimens require specific supportive care to mitigate serious toxicities and are best delivered at centres with lymphoma expertise. HD-MTX should be given as a short infusion (over 2–4 hours) at a dose of ≥3g/m^2 to optimize delivery across the blood-brain barrier (BBB).

HD-MTX can generally be given at full doses if the creatinine clearance is ≥50mL/min; dose adjustments or alternative therapies should be considered if the creatinine clearance is lower or if there are other risk factors for MTX toxicity.[12]

Decision-making for treatment can be initially informed by a patient's potential fitness for TT-ASCT (**Figure 1**). This is a clinical judgement based on a composite of age, organ function, comorbidities, and Eastern Cooperative Oncology Group performance status (ECOG PS) (considering both premorbid and lymphoma-related PS). For patients whose fitness for TT-ASCT is uncertain at initial diagnosis, re-evaluation should be undertaken dynamically during the early remission induction phase. **Table 1** summarizes the results of key clinical trials informing current treatment approaches.[13]

Younger Patients Fit for Intensive Treatment

Intensive remission-induction therapy with the intention to proceed to full-dose TT-ASCT should be considered in fit patients up to the age of 70. In this population, clinical trials have demonstrated improved event-free survival, quality of life, and neurocognitive outcomes with TT-ASCT compared to WBRT consolidation,[1,2] and improved overall survival (OS) with TT-ASCT compared to consolidation with further conventional dose chemotherapy.[14]

Various induction regimens, centred around a rituximab and HD-MTX backbone, have been demonstrated to be efficacious in large prospective trials. Based on the randomized IELSG32 trial, the preferred approach in many countries is four cycles of MATRix (HD-MTX, high-dose cytarabine [HD-AraC], thiotepa, and rituximab), followed by BCNU/TT-ASCT consolidation.[1] Importantly, real-world data suggest the IELSG32 approach should only be considered for patients who would have been trial-eligible (age ≤65 years and ECOG PS ≤3 or 66–70 years and ECOG PS ≤2). In a real-world European and UK study, patients with age or ECOG PS outside of IELSG32 eligibility criteria experienced first-cycle intensive care unit (ICU) admission rates of 11%, compared to 5% for IELSG32-eligible patients; the overall MATRix-related treatment-related mortality (TRM) was 6%.[15] Institutional experience with the required supportive care and expected toxicity of MATRix, including dose reductions, likely results in improved outcomes. A 25% dose reduction of cytarabine (i.e., omission of one dose) should be considered if the preceding cycle was complicated by febrile neutropenia.[16]

TT-ASCT is generally considered for patients with non-progressive disease (complete remission [CR], partial remission [PR], or stable disease [SD]); while also feasible in the setting of progressive disease (PD), these patients have poorer survival outcomes.[2] A reasonable alternative approach for patients with PD is to use a non-cross-resistant chemotherapy regimen (e.g., RICE [rituximab, ifosfamide, carboplatin, etoposide] or TIER [thiotepa, ifosfamide, etoposide, rituximab])[16,17] or WBRT, in order to improve response status prior to ASCT. Full-dose thiotepa (20mg/kg) conditioning is generally recommended in younger, fit patients. Although retrospective data show that 10mg/kg thiotepa (TT10-ASCT) may achieve equivalent outcomes

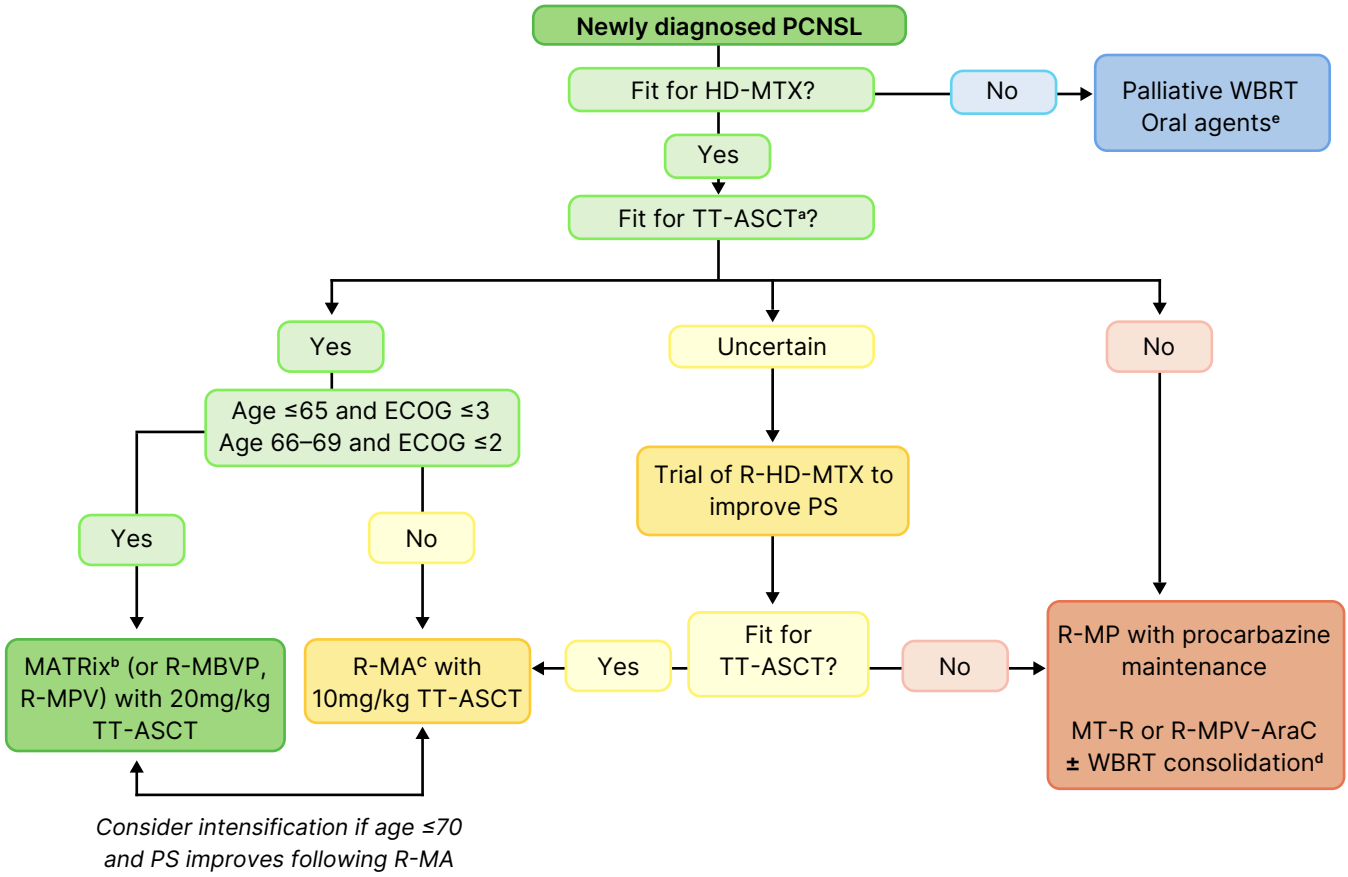

Figure 1. Suggested treatment algorithm for newly-diagnosed PCNSL; *courtesy of Diva Baggio, MD and Chris P. Fox, MBChB, FRCP, FRCPath, PhD.*

[a]Dynamic re-assessment of fitness for transplant should be performed at each clinical review.
[b]MATRix preferred due to randomised data.
[c]Consider empiric dose-reduction to two or three (rather than four) doses of cytarabine per cycle, and increasing total cycles to 3-4, particularly for patients with uncertain fitness for TT-ASCT.
[d]The PFS benefit of WBRT should be weighed against the risk of possible neurotoxicity and impact on quality of life.
[e]Options include palliative temozolomide, lenalidomide, or Bruton tyrosine kinase inhibitors.

Abbreviations: HD-MTX: high dose methotrexate; **TT-ASCT:** thiotepa autologous stem cell transplant; **WBRT:** whole brain radiotherapy; **MATRix:** methotrexate, cytarabine, thiotepa, rituximab; **R-MBVP:** rituximab, methotrexate, BCNU, etoposide, prednisolone; **R-MPV(-AraC):** rituximab, methotrexate, procarbazine, cytarabine; **R-MA:** rituximab, methotrexate, cytarabine; **R-MP:** rituximab, methotrexate, procarbazine; **MT-R:** methotrexate, temozolomide, rituximab

compared to 20mg/kg[18], a dose also supported by prospective studies in patients ≥65 years[4], prospective studies in younger patients are lacking. BEAM (BCNU, etoposide, cytarabine, melphalan) and other non-TT-containing regimens are not recommended due to lower efficacy in CNS lymphoma.[19]

Older Patients Fit for Intensive Treatment

Older fit patients eligible for TT10-ASCT may be considered for the MARTA treatment paradigm.[4] This single-arm, Phase II study of patients ≥65 years demonstrated the feasibility of TT10-ASCT as consolidation for patients in CR/PR/SD following two cycles of R-MA (rituximab, HD-MTX, HD-AraC). Rituximab/busulfan/thiotepa

(rather than BCNU/TT) conditioning was used based on a pilot study demonstrating tolerability in older patients.[20] Median PFS was 41.1 months (compared to 3.1 months in the 15 patients who did not achieve ASCT), with cumulative non-relapse mortality (NRM) of 14% at 3 years in a per-protocol analysis.

Only two doses of HD-MTX are delivered with the MARTA approach, but this is accompanied by dose-intensive AraC (four 2g/m^2 doses per cycle); relevant to observed toxicities. One-third of patients experienced grade ≥3 infections, including 2 (4%) deaths from infection and a total NRM of 9% during the induction phase. Where fitness for the MARTA approach is unclear, a reasonable initial approach is to deliver an initial cycle of R-HD-MTX to improve ECOG PS and potentially allow intensification with the R-MA regimen for subsequent cycles. This concept is analogous to the currently-recruiting OptiMATe trial for patients ≤70 years.[21] For 'borderline' cases, our practice is to pre-emptively reduce the cytarabine to 2 or 3 doses per cycle whilst increasing the number of cycles delivered to 3–4. However, it is currently unclear whether this empirical approach will confer a similar level of efficacy as the original MARTA protocol.

Patients Unfit for TT-ASCT

For patients considered to be unsuitable for TT-ASCT consolidation, less intensive HD-MTX-based regimens are typically employed as remission induction. Consolidation approaches include 'maintenance' therapy, surveillance only (for those in CR), or WBRT in carefully selected patients with shared decision-making regarding risks and benefits.

The single-arm Phase II PRIMAIN study examined the efficacy of three cycles of R-MP (rituximab, HD-MTX, procarbazine) followed by 6 cycles of oral procarbazine maintenance (100mg for 5 days every 4 weeks; see **Table 1**) in patients ≥65.[22] The oldest enrolled patient in PRIMAIN was 85 (median age 73), and the 2-year OS was 48%, with a median OS 22.6 months. TRM was 2/38 (5%) amongst patients treated with R-MP. A prior protocol version, which included a fourth drug, lomustine (R-MPL), conferred a much higher TRM of 7/69 (10%) and is therefore not recommended.

(R-)MPV-AraC (rituximab, HD-MTX, procarbazine, vincristine, HD-AraC) represents another common induction regimen. The ANOCEF-GOELAMS Phase II randomized study of patients ≥65 years compared two remission induction regimens, either MPV-AraC or MT (methotrexate, temozolomide), without maintenance or consolidation.[23] OS for patients treated with MPV-AraC was numerically higher without statistical significance (2-year OS 58% vs. 39% for MPV-AraC vs. MT, respectively), without differences in grade 3–4 toxicity.

RTOG 1114 was a randomized study of four cycles of R-MPV-AraC without consolidation *versus* R-MPV-AraC followed by reduced-dose WBRT consolidation (rdWBRT; 24.3Gy). The median age was 63 years (range 21–84). The primary study data have not yet been published in full manuscript form, although a superior 2-year PFS in favour of the chemo-radiotherapy arm has been presented in abstract form (78% versus 54%; HR 0.51, p=0.015).[24] Given neurotoxicity concerns associated with combining HD-MTX and WBRT, this approach should only be considered after careful discussion; final study results (including formal cognitive and quality of life assessments) from RTOG 1114 will further inform decision-making.

Patients Unfit for HD-MTX

A minority of patients are unfit for HD-MTX.[11] Options for these patients include palliative WBRT, palliative oral chemotherapy (e.g., temozolomide), or best supportive care. Data from studies of lenalidomide or Bruton's tyrosine kinase inhibitors in the refractory/relapsed setting may support consideration of these agents, which may be off-label within a patient access scheme, if available.

PCNSL in People Living with HIV

HIV-associated PCNSL typically occurs in the setting of severe CD4+ lymphopenia. Tumour cells are invariably positive by Epstein-Barr encoding region (EBER) *in situ* hybridization (ISH).[8,25] In patients with CD4+ lymphopenia, the recommended treatment is six infusions of R-HD-MTX, together with antiretroviral therapy (ART). With this approach, the 5-year OS was 67% in a prospective study.[25] More intensive PCNSL regimens are generally not appropriate in this setting, given toxicity risks and the additional therapeutic effect of ART-associated immune reconstitution. Occasionally, patients with well-controlled HIV, without CD4+ lymphopenia, are diagnosed with EBV-negative PCNSL, for whom treatment should follow the recommendations for immunocompetent individuals.

Study	*N*	Inclusion criteria	Induction	Consolidation	CR rate post-induction	PFS/OS	TRM
IELSG32 (Phase II randomised; two randomisations) *NCT01011920*	219	18–70 years of age ECOG score ≤3 if ≤65 years ECOG score ≤2 if 66-70 years	4 cycles, randomised 1:1:1 of one of the following: **Group A:** MA **Group B:** R-MA **Group C:** MATRix	Patients in CR/PR randomised 1:1 (post induction) to one of the following: **Group D:** WBRT (36Gy if in CR; +9Gy tumour boost if in PR) **Group E:** BCNU/TT ASCT	CR rate post 4 cycles of MATRix: 49% (statistically superior to other arms)	Statistically superior 7-year PFS (52%, 95% CI 47-57) and OS (56%, 95% CI 52–60) observed for MATRix induction No significant difference PFS and OS observed for WBRT and ASCT; quality of life and neurocognitive testing statistically superior for ASCT	MATRix-treated patients (including death during induction or consolidation): 4% Post ASCT (all induction regimens, per-protocol): 5%
PRECIS (Phase II randomised) *NCT00863460*	140	18–60 years of age Any ECOG	2 cycles of R-MBVP followed by 2 cycles of R-AraC (AraC 3g/m^2/day for 2 days each cycle; rituximab 375mg/m^2 once per cycle)	Patients randomised 1:1 (prior to induction) to one of the following, and proceeded regardless of response following induction: **Arm A:** WBRT (40Gy) **Arm B:** Bu/Cy/TT ASCT	CR/CRu rate post R-MBVP/R-AraC induction: 43%	Statistically superior 8-year EFS observed for ASCT (67%, 95% CI 55-83) compared to WBRT (39%,95% CI 27–57) No significant OS difference observed	Post ASCT (per protocol): 11%
IELSG43 "MATRix" (Phase III randomised) *NCT02531841* *Reported in abstract*	346	18–70 years of age Any ECOG if ≤65 years ECOG score ≤2 if 66-70 years	4 cycles of MATRix	Patients in CR/PR randomised 1:1 (post induction) to one of the following: **Arm A:** 2 cycles of R-DeVIC **Arm B:** BCNU/thiotepa ASCT	CR rate following 4 cycles of MATRix: 27%	Despite similar CR rates post consolidation with R-DeVIC and ASCT, statistically superior 3-year outcomes were observed post ASCT in both PFS (79%, 95% CI 71–86) and OS (86%, 95% CI 78–91)	During induction 4% Post ASCT (per protocol): 4%
RTOG 1114 (Phase II randomised) *NCT01399372* *Reported in abstract*	87	≥18 years of age KPS ≥50 (or 30–50 if due to lymphoma)	4 cycles of R-MPV (vincristine omitted in cycles 3 and 4)	Patients randomised 1:1 (prior to induction) to one of the following: **Arm A (chemotherapy only):** 2 cycles of AraC (3g/m2/day for 2 days each cycle) **Arm B (chemo-radiotherapy):** reduced dose WBRT (total dose of 23.4Gy), followed by 2 cycles of AraC with doses as above *Patients in CR/PR/SD proceeded to rdWBRT; those with PD came off study*	Not reported	Statistically superior 2-year PFS demonstrated for chemo-radiotherapy (78%) versus chemotherapy only (54%)	One death from sepsis reported in the chemotherapy arm
MARTA (Phase II, single arm) *DRKS00011932*	51	≥65 years of age ECOG ≤2 (or ≤3 if attributable to lymphoma) Eligible for ASCT	2 cycles of R-MA	Patients in CR/PR/SD proceeded to R/Bu/TT ASCT	CR/CRu in 12% PR in 71% ASCT performed in 36 patients (71%)	1-year PFS 59% (95% CI 44–71%)	NRM during induction (per protocol): 9% NRM post ASCT (per protocol): 5%

Study	*N*	Inclusion criteria	Induction	Consolidation	CR rate post-induction	PFS/OS	TRM
PRIMAIN (Phase II, single arm) *NCT00989352*	107	≥65 years of age Any ECOG	3 cycles of R-MP(L) (lomustine administered to n=69; subsequently removed for the remaining n=38 due to TRM)	No consolidation Maintenance therapy with 6 cycles of procarbazine 100mg for 5 days, repeated every 28 days	CR rate with R-MP: 32%	Overall 2-year PFS and OS were similar with R-MP and R-MPL 2-year PFS with R-MP: 35% (95% CI 19–50) 2-year OS with R-MP: 48% (95% CI 30–65)	R-MPL: 10% R-MP after protocol amendment: 5%
ANOCEF-GOELAMS (Phase II, randomised) *NCT00503594*	95	≥60 years of age KPS ≥40	Patients randomised 1:1 to one of the following: **Arm A:** 3 cycles of MT **Arm B:** 3 cycles of MPV and 1 cycle of AraC (3g/m2/day for 2 days)	No consolidation	Numerically higher CR/CRu rate with MPV-AraC (62%) to MT (45%)	Numerically but not statistically higher 2-year OS with MPV-AraC (58%, 95% CI 43–72%) than MT (39%, 95% CI 26–53)	MT: 10% MPV-AraC: 6%

Table 1. Select clinical trials in newly diagnosed PCNSL[1, 2, 3, 13, 21, 22, 23]; *courtesy of Diva Baggio, MD and Chris P. Fox, MBChB, FRCP, FRCPath, PhD.*

Chemotherapy doses of specific induction regimens:
(R-)MA (IELSG32, MARTA): methotrexate 3.5g/m^2 ; cytarabine 2g/m2 (4 doses per cycle) ± rituximab 375mg/m^2 (2 doses per cycle)
MATRix (IELSG32, IELSG43): methotrexate 3.5g/m^2 ; cytarabine 2g/m2 (4 doses per cycle); thiotepa 30g/m^2 ; rituximab 375mg/m^2 (2 doses per cycle)
R-MBVP (PRECIS): rituximab 375mg/m2; methotrexate 3g/m^2 (2 doses per cycle); etoposide 100mg/m^2; BCNU 100mg/m^2 ; prednisolone 60mg/m^2/day for 5 days
R-MPV (RTOG 1114): rituximab 500mg/m2 (2 doses per cycle); methotrexate 3.5g/m^2 (2 doses per cycle); vincristine 1.4mg/m^2 (dose capped at 2.4mg, 2 doses per cycle; given in cycles 1–2 only); procarbazine 100mg/m^2/day for 7 days
R-MP(L) (PRIMAIN): rituximab 375mg/m^2; methotrexate 3g/m^2 (3 doses per cycle); procarbazine 60mg/m^2/day for 7 days; ± lomustine 110mg/m2 for one dose
MT (ANOCEF-GOELAMS): methotrexate 3.5g/m^2 (2 doses per cycle); temozolomide 150mg/m2/day for 5 days in cycle 1 and 10 days in cycle 2 and 3
MPV (ANOCEF-GOELAMS): methotrexate 3.5g/m^2 (2 doses per cycle); vincristine 1.4mg/m2 (dose capped at 2.8mg, 2 doses per cycle); procarbazine 100mg/m2/day for 7 days

Chemotherapy doses of specific consolidation and conditioning regimens:
R-DeVIC (IELSG43): rituximab 375mg/m^2 ; dexamethasone 40mg (3 doses per cycle) ; etoposide 100mg/m2 (3 doses per cycle), ifosfamide 1500mg/m2 (3 doses per cycle); carboplatin 300mg/m^2
BCNU/TT conditioning (IELSG32, IELSG43): BCNU 400mg/m2 ; thiotepa 20mg/kg divided in 4 doses over 2 days
Bu/Cy/TT conditioning (PRECIS): thiotepa 250mg/m^2/day for 3 days ; busulfan 8mg/kg ; cyclophosphamide 120mg/kg divided in 2 doses over 2 days
R/Bu/TT conditioning (MARTA): rituximab 375mg/m^2 ; busulfan 6.4mg/kg divided in 2 doses over 2 days ; thiotepa 10mg/kg divided in 2 doses over 2 days

Abbreviations: CR: complete remission; **CRu:** unconfirmed complete remission; **PR**: partial remission; **PFS:** progression-free survival ; **OS:** overall survival; **EFS:** event-free survival; **TRM:** treatment-related mortality; **ASCT:** autologous stem cell transplant; **WBRT:** whole brain radiotherapy

Concomitant Vitreoretinal Involvement in PCNSL

Vitreoretinal lymphoma is rare, and high-quality evidence to guide treatment is lacking. The systemic agents used in PCNSL have vitreoretinal activity, and in cases of concomitant VRL, a similar treatment paradigm can be applied. Intravitreal chemotherapy injections are not routinely recommended but may have a role in frail patients who are HD-MTX-intolerant. Response in the ocular compartment should be assessed with serial slit-lamp examinations in addition to brain imaging. Consolidation ocular radiotherapy can be considered, with the decision and dose informed by end-of-treatment response.[6,9]

Response Assessment and Surveillance

Response assessment typically follows the International Primary CNS Lymphoma Collaborative Group (IPCG) consensus[26], initially published in 2005 for benchmarking and consistency within clinical trials. With modern PCNSL treatment paradigms, response assessment is recommended every 2 cycles, prior to and following consolidation (after 1–2 months).[16]

The role of surveillance MRI following completion of therapy is less clear. IPCG guidelines recommend surveillance every 3 months for 2 years, 6 months for 3 years, and annually for at least 5 years. Clinical surveillance—including patient education—at these later time points may be sufficient in routine practice.[26] However, MRI surveillance may be particularly important in patients with residual imaging abnormalities on end-of-treatment MRI. Neurocognitive function generally improves with disease response, although it often lags radiological findings. However, late neurotoxicity is observed both following HD-MTX and, more commonly, after radiation-based approaches.[2] Where available, all patients should be referred for formal neuropsychologic assessment as part of a holistic approach to survivorship.

Conclusion

The modern treatment paradigm of PCNSL prioritizes R-HD-MTX-containing chemotherapy for remission induction and is partnered with other CNS-active agents according to patient fitness and institutional protocol experience. Consolidation therapy is key to survival outcomes in PCNSL and TT-ASCT should be pursued in all eligible patients. With this approach, long-term remissions are observed in over half of patients undergoing TT-ASCT. However, of all patients diagnosed with PCNSL, a majority experience relapse, most of whom will die from their disease. This clearly highlights an unmet need in PCNSL, notwithstanding recent therapeutic progress. Ongoing trials are focused on improving the safety and efficacy of first-line regimens. However, a further paradigm shift will require improved prognostication and more sensitive and specific measures of disease activity, which is an area of active investigation. More focus on neurocognitive function and survivorship is also needed and should be embedded as key outcome measures in prospective trials.

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Financial Disclosures

D.B.: None declared.
C.P.F.: None declared.

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