PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

CENTRAL NERVOUS SYSTEM

LYMPHOMA

Primary CNS lymphoma Treatment Policies 2020

1 . Introduction and Prevention

Primary central nervous system DLBCL is a rare and aggressive B-cell malignancy defined by involvement of the brain, leptomeninges, eyes, or spinal cord in the absence of systemic disease. It accounts for 1% of all non-hodgkin lymphomas and 3% of all brain tumours. Risk factors for the development of PCNS DLBCL include increasing age and immunocompromised states, in particular HIV, which has been reported to be associated with a 3600-fold increased risk compared with the general population.

2. Diagnosis and pathology

Patients are treated based on a diagnosis conforming to World Health Organization criteria, most often after primary evaluation or pathology review by an expert Hematopathologist at the University Health Network. A histological or cytological diagnosis is required, MRI findings alone are not sufficient. A stereotactic biopsy of a brain lesion is recommended. Where biopsy is not possible, MRI findings supported by CSF or vitreous fluid demonstrating large clonal B cells by flow or PCR may make the diagnosis. Corticosteroids should be avoided prior to biopsy, if possible. If a suspected PCNSL lesion resolves following steroid administration, re-imaging with MRI should be performed after a short interval with a view to urgent biopsy at lesion re-growth. Vitreous biopsy should ideally be combined with a subretinal aspirate or chorioretinal biopsy to establish a diagnosis of primary intraocular lymphoma (PIOL).

The diagnosis of diffuse large B-cell is made by histology and immunophenotypic analysis using a panel of antibodies:

CD5, CD10, CD20, CD23, CD30, BCL6, BCL2, MYC, MUM1, KI67, CCND1 and EBER.

The panel includes markers that distinguish between prognostic subgroups of diffuse large B-cell lymphoma, NOS. Prognostic subgroups comprise those with the immunophenotype of activated B-cells (ABC) and of germinal centre B-cells (GCB), the former having a worse prognosis than the latter. In addition, the expression CD5 or the co-expression of BCL2 and MYC protein, with respective cut offs of 50% and 40%, are also considered adverse prognostic markers. Additionally, all lymphoma with the histology of diffuse large B-cell lymphoma or high grade B-cell lymphoma are tested for MYC gene translocation by fluorescence in situ hybridization (FISH). Those cases showing MYC gene translocation are further tested for BCL2 and BCL6 gene translocation, in order to properly diagnose high grade B-cell lymphoma with MYC translocation and BCL2 or BCL6 translocation.

References:

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon, France: IARC Press; 2008

3. Staging Investigations

- Contrast enhanced MRI (including diffusion sequences) of brain and spine at baseline and for response assessment. Neuroaxis imaging (brain and entire spinal cord) should be reviewed by a specialist neuroradiologist.

- Full history and physical examination including performance status and testicular exam in males

- Cognition evaluation (MMSE, miniCOG, or MoCA)

- CBC, albumin, LDH, LFTs (bilirubin, ALT, AST, ALP), creatinine,

- CT Head and Neck, thorax, abdomen, pelvis, testicular ultrasound

- FDG-PET/CT desirable, but not required, esp as patients are usually acutely unwell or admitted as inpatients as they start therapy

- HBsAg, HBsAb, HBcoreAb; HCV antibody, HIV

- Ophthalmological examination

- Lumbar puncture for protein, glucose, cell count and cytology/flow cytometry is desirable, but not necessary.

- BM aspirate and biopsy for morphology, immunohistochemistry, flow cytometry can be omitted if will delay treatment or if a PET/CT is available with no evidence of bone marrow involvement and normal CBC

(Table below from the British Society of Hematology PCNSL guidelines. Fox et al. BJH. 2019)

Table I. Pre-treatment investigations and staging for primary central nervous system lymphoma.

	Histology	Imaging	Clinical evaluation	Laboratory evaluation	CSF analysis*
Essential	Tissue diagnosis: a) Stereotactic or surgical biopsy b) Vitrectomy specimen (if PIOL suspected) c) CSF (if no other diagnostic material)	Gadolinium-enhanced MRI brain and spine* Systemic cross-sectional imaging (PET-CT preferred but contrast-enhanced CT of neck to pelvis acceptable) Testicular ultrasound	Physical examination including full neurological assessment Full medical history and drug history, including corticosteroid use Performance status Ophthalmological examination with fundoscopy and slit-lamp examination Baseline MMSE	Renal and liver function Serum LDH Creatinine clearance HIV, hepatitis B (including core Ab) and C serology	
Desirable	Bone marrow trephine and aspirate†	Whole body FDG-PET† Assessment of LVEF if indicated	Formal neuropsychological assessment (see Table II)		CSF protein Cytology assessment

4. Treatment approaches

<u>Patients transplant eligible, ≤70 yrs of age</u>

MATRIX chemotherapy X 4 cycles, followed by consolidation with autologous stem cell transplantation (as per the IELSG32 study)

MATRIX x 2 cycles → MRI at least PR (or close to) → MATRIX 3rd cycle (omit thiotepa) with stem cell mobilization of the chemotherapy cycle→complete MATRIX 4th cycle→ ASCT (BCNU and thiotepa conditioning)

Combination chemotherapy with high-dose methotrexate (HD-MTX), cytarabine (AraC), thiotepa, and rituximab (MATRix regimen) is recommended as first-line treatment of PCNS DLBCL for patients younger than 70 years with adequate renal function (CrCl >50ml/min).

Age < 70 years, no co-morbidities precluding intensive therapy: plan for autologous stem cell transplantation (ASCT)

Toxicity can be high with this regimen, thus close followup with twice weekly bloodwork is recommended between cycles, as well GCSF prophylaxis (Grastofil 300ug sc daily X 7 days, starting D6), PJP prophylaxis with Septra SS 2 tabs qMWF and Acyclovir 400mg po bid/Valacyclovir 500mg po daily.

In a recent real world study, chemotherapy modifications were more frequent (40–50%) but survival rates were similar to those in IELSG32, with 2-year OS of 64%. Severe infectious complications and intensive care support were more common during cycle 1 (16%) than cycle 4 (5%). Thus, for patients considered at risk of increased toxicity (any of: ECOG performance status ≥2, co-morbid conditions or age >65 years) we recommend dose reducing the myelotoxic agents in MATRix (cytarabine and thiotepa) for the initial cycle, with dynamic review cycle by cycle. In practice, a 25% reduction of cytarabine (achieved by omitting the 4th dose in the cycle) with or without a 25% dose reduction of thiotepa is a reasonable strategy.

The additional value of concurrent intrathecal chemotherapy is unproven, thus given the improved efficacy of systemic therapy, we do recommend the concurrent use of intrathecal treatment.

Ideally, the 2 or 3rd cycle of MATRIX chemotherapy will be used to mobilize stem cells with high dose GCSF starting on Day 6. Mobilizing using the fourth cycle or beyond becomes much more difficult, and we have noticed omitting the thiotepa significantly improves stem cell mobilization efficiency. Thus, if feasible, this will be considered.

Patients who have had at least a PR after 3-4 cycles of MATRIX, and are otherwise eligible for ASCT based on organ, performance and neurocognitive status and patient wished, will have their response consolidated with BCNU and Thiotepa conditioning and ASCT.

If patients do not have an adequate response to MATRIX (PR or better) or progress on treatment, can be considered for salvage with ICE chemotherapy X 2cycles, with an intent of still reaching an autologous stem cell transplantation if a PR or better is achieved. However, this should be considered on a case-by-case basis, as the chance of response is <30%, and should only be considered, in younger, fit patients, who otherwise have an excellent performance status and no other comorbidities.
Salvage WBRT should be strongly considered in the setting of refractory disease.

Patients who: 1) are not felt to be eligible for salvage chemotherapy or progress on it; 2) have residual disease post-induction chemoimmunotherapy and are ineligible for ASCT (or choose not to have it); or 3) residual disease after thiotepa-based ASCT; should be treated with whole brain radiotherapy (WBRT), in consultation with a radiation oncologist with expertise in CNS lymphoma.

WBRT

When radiation is employed, whole brain radiotherapy (WBRT) is required as part of the treatment because lymphoma involvement is always more extensive than what is visible on MRI.

Indications for radiotherapy include:

- Consolidation treatment:
    - As an alternative consolidation treatment to stem cell transplant
    - For younger patients who received standard methotrexate-based chemotherapy without transplant
- Definitive treatment:
    - Definitive therapy for patients of any age who are ineligible for chemotherapy
- Refractory disease:
    - Progressive disease on chemotherapy
    - Residual disease after chemotherapy
- Relapsed disease:
    - Progressive disease after completion of chemotherapy

The standard WBRT dose for curative-intent treatment 36 Gy WBRT. A boost to 45 Gy of enhancing tumour may be considered in select cases, but is optional. In patients with CR after standard methotrexate-based chemotherapy without transplant, 23.4 Gy WBRT may be considered in selected patients, ideally on a study.

Radiation, as a consolidation treatment, should be used in caution amongst patients older than 65-70 due to the risk of late neurocognitive toxicity.

Radiation, as a definitive (no chemotherapy) treatment, can be dose-escalated from 36 Gy WBRT to 45 Gy WBRT in selected patients (Yahalom, IJROBP 2015).

WBRT fields should be designed with coverage of the posterior orbits and optic nerves.

Patients transplant ineligible, >70 yrs of age or due to comorbidities, but still eligible for HDMTX based therapy (adequate renal function and ECOG performance status ≤3)

R-MVP (rituximab, methotrexate, vincristine and procarbazine) q14 days X 5 cycles (as per the DeAngelis protocol), followed by Ara-C consolidation q28 days X 2 cycles.

HD-MTX+rituximab alone

Prospective, randomized trials evaluating elderly patients with PCNSL are lacking; thus,the optimal chemotherapy regimen in this population is not clear. Single-agent HD-MTX and HD-MTX-based combination regimens, including the MATRix regimen, may be reasonable options particularly in fit patients with an ECOG performance status ≤3 (CCO guideline, 2017). Based on previous experience in Toronto with the De Angelis protocol, we recommend this approach for patients not eligible for upfront consolidation with a transplant, due to the upfront toxicity of MATRIX.

Regardless of regimen chosen, HD-MTX should be given at doses of at least 3g/m2 with an infusion time of 2-4h, for a minimum of 4 cycles at 2 to 3 wk intervals.

Elderly patients with PCNS lymphoma and reduced renal function are at increased risk for MTX-related toxicity. The use of MTX in patients with creatinine clearance lower than 50 ml/min has not been adequately evaluated in prospective studies. Physicians should consider the issue of renal function and the potential for increased HD-MTX toxicity in elderly patients (CCO guideline, 2017).

R-MVP q14 days X 5 cycles, Cytarabine consolidation q28 days X 2 cycles.

Phase	Drug	Dose	Timing
Induction	Rituximab	375mg/m2	D1
	Methotrexate	3500mg/m2	D2
	Vincristine	1.4mg/m2 (max2)	D2 (cycles 1,3,5)
	Procarbazine	100mg/m2 (rounded to nearest 50mg)	D1-7 (cycles 1,3,5)
Consolidation	Cytarabine	3000mg/m2/day	D1,2

As above:
Patients who: 1) are not felt to be eligible for salvage chemotherapy or progress on it; 2) have residual disease post-induction chemoimmunotherapy and are ineligible for ASCT (or choose

not to have it); or 3) residual disease after thiotepa-based ASCT should be treated with WBRT, in consultation with a radiation oncologist with expertise in CNS lymphoma.

Patients ineligible for HDMTX, consider one or a combination of treatments below:
1. Whole brain radiotherapy (dosing and fractions chosen by a radiation oncologist with expertise in CNS lymphoma, based on performance status, therapeutic aims and life expectancy)
2. Oral chemotherapy (ibrutinib or lenalidomide if accessible)
3. Temozolomide
3. Steroids (dexamethasone)

Whole brain radiotherapy (WBRT) or comfort-based palliative care are reasonable treatment options for patients who refuse aggressive chemotherapy or who are considered ineligible for HD-MTX-based, or alternative, chemotherapy regimens.
The clinical benefit of WBRT in this poor-risk population, compared with supportive care, has not been confirmed in prospective comparative clinical trials. WBRT as a sole treatment modality is associated with a response rate of approximately 50% and median survival of approximately one year that is offset by a risk of neurotoxicity. A patient-centred, multi-disciplinary approach should be utilized prior to initiating WBRT. (CCO guideline, 2017)

Pallative-intent WBRT regimens include 20 Gy in 5 fractions or 30 Gy in 10 fractions.

Primary intraocular lymphoma
In patients with PIOL who are candidates for chemotherapy, treatment that includes HD-MTX should be considered. Patients that are ineligible for systemic chemotherapy should be treated with a local approach, either intravitreal chemotherapy or ocular radiation.
The optimal management of PIOL is not known due to a lack of prospective ans comparative data. HD-MTX-based systemic chemotherapy and local approaches (intravitreal methotrexate, ocular radiation) are both reasonable options for treatment. Given the improvement in outcomes for patients with PCNSL treated with HD-MTX-based chemotherapy, and recognizing the relatively high relapse rates in PIOL treated with local approaches, we recommend that HD-MTX-based chemotherapy should be considered for eligible patients with PIOL. For fit patients, MATRIX followed by consolidation with thiotepa-based ASCT OR bilateral orbital radiotherapy, is reasonable.

Response assessment and follow-up
Consider MRI assessment after cycle 1 in transplant eligible patients, to inform timing of stem cell mobilization.
Every 2 cycles otherwise and at the end of induction therapy to assess remission status. If proceeding on to ASCT, MRI assessment pre-ASCT and 3 months post.
If in remission, every 3 months for 1 yr, every 6 months for 1 yr, then at clinician's discretion.
Neurocognitive assessments (miniCOG at end of treatment and q3-6 months)

Second line:

Refractory disease after induction chemo

- Very Fit on a case-by-case basis: ICE X 2cycles then ASCT if PR or better.

Refractory disease after ASCT, or not fit for ICE:

- WBRT +/- ocular rads if ocular involvement

Relapse:

- Repeat biopsy if atypical MRI appearance or new brain lesion >2y after initial therapy
- Repeat staging
- If eligible for intensive treatment:
  Re-induction:
  - If prolonged response (>24months) to initial MTX-containing regimen, consider repeating MTX-based regimen
  - If <24 months: consider R-ICE

  Consolidation:
  - If previous ASCT: WBRT if age <60 or age >60 and not in CR can be considered vs. omission of consolidation in select patients who are not in CR after discussion of risks and benefits at MCC.
  - If previous WBRT: ASCT
  - Omission of consolidation can be considered in select cases.

If not a candidate intensive therapy, consider:

- Ibrutinib
- Lenalidomide
- Palliative options above (temozolomide, WBRT, steroids, palliative care)

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