Lancashire and South Cumbria Guideline for Management of Primary CNS Diffuse Large B-cell Lymphoma (PCNSL)

1.1 Pretreatment evaluation

1.2

- The diagnosis of PCNSL should be made on a brain biopsy, CSF cytology or in the case of intra-ocular lymphoma a vitreous or chorioretinal biopsy.
- Management will be based on the diagnosis made following expert haematopathology review at HMDS Leeds, or in the case of ocular lymphoma review at the Department of Ocular Pathology, Liverpool.
- Note pre-diagnostic biopsy steroids should be avoided where possible.

1.3 The following tests should be performed:

- Contrast-enhanced MRI scan of brain
- Ophthalmological assessment with slit-lamp examination followed where necessary by vitreous biopsy +/- chorioretinal biopsy to exclude intra-ocular involvement.
- PET-CT scan, or CT scan neck, thorax, abdomen if PET not possible
- Bone marrow aspiration and trephine biopsy if PET-CT scan suggests bone marrow infiltration or if PET-CT scan is not possible.
- CSF cytospin and protein estimation where feasible.
- Testicular ultrasound scan
- FBC, U&Es, creat, LFTs, calcium, LDH, urate, immunoglobulins and electrophoresis
- Hepatitis B, C and HIV serology
- ECG and assessment of cardiac function
- Establish fitness for intensive therapy and high dose methotrexate based on age comorbidity and physiological factors
- Calculation of PCNSL prognostic score (See Appendix)

1.4 Where appropriate patients must be offered referral for reproductive counselling, and sperm cryopreservation/oocyte harvesting/ovarian preservation prior to commencing potentially gonadotoxic therapy.

1.5 All new and relapsed cases must be discussed at the regional Lymphoma MDT prior to commencing treatment. If there is an urgent need to start treatment prior to the next MDT, the case must be discussed with an MDT Core Member.

2.0 Post-treatment evaluation

- On completion of treatment the patient must be reassessed clinically and with a repeat MRI scan of brain, +/- ophthalmic examination +/- CSF cytospin examination followed by MDT review
- Patients on high-dose methotrexate regimens should have a contrast-enhanced MRI scan of brain after every 2 cycles (and consider after cycle 1 if PBSC mobilisation is planned after cycle 1). An MRI scan should also be performed three months after completing any consolidation therapy.

3.0 First line treatment

3.1 Patients eligible for induction with intensive combination chemo-immunotherapy incorporating high-dose methotrexate e.g MATRIX

- If the patient presents with impaired performance status but it is considered they may be candidates for intensive MATRIX chemotherapy, consider an initial cycle of rituximab and high dose methotrexate, then review.
- Note MATRIX chemotherapy is poorly tolerated in patients over 70 years.

3.2 If considered sufficiently fit for MATRIX:

- MATRIX regimen x 4 cycles (with 3.5g/m^2 methotrexate over 4hours) if responsive after cycle 2.
- Consider a 25% dose reduction with cycle 1 for patients with poor performance status e.g ECOG score ≥2, age >65 years, and/or significant comorbidity.
- Plan or PBSC mobilisation following 2nd cycle MATRIX.

3.3 Consolidation therapy following intensive induction

Following cycle 4 MATRIX and if there is at least stable disease, performance status and organ function should be reviewed:

If considered sufficiently fit advise consolidation with autologous stem cell transplant (ASCT) conditioned using high dose thiotepa and BCNU.

- Consolidation whole brain radiotherapy (WBRT) should be considered for those not in CR following ASCT.
- If not fit for transplant and not in CR following four cycles MATRIX advise consolidation whole brain RT (WBRT).
- If not fit for transplant and in CR the potential for improved progression free survival following WBRT must be balanced against the risk of neurocognitive impairment on an individual basis. In general RT should be avoided in patients > 60 years.
- RT should be given at a dose of 30Gy in 20 fractions and consider a 9Gy boost with a 1-2cm margin to residual enhancing lesions. Consider a lower dose of 23.4Gy in patients at higher risk of neurotoxicity.
- Consider also bilateral ocular RT if there was concurrent ocular lymphoma and the patient did not undergo ASCT, or was not in CR following ASCT.

3.4 Patients who are fit for high dose methotrexate but not fit for an intensive MATRIX and ASCT.

Options are:

- Induction with two cycles of rituximab, high dose methotrexate 3.5g/m^2 and cytarabine 2g/m^2 bd for two days (MARTA regimen) followed by consolidation with ASCT conditioned with rituximab, thiotepa and busulphan.
- Six cycles of rituximab, methotrexate 3.5g/m^2 and procarbazine followed by maintenance procarbazine in those with at least stable disease (PRIMAIN regimen).
- Consider consolidation WBRT and/or ocular RT as in 3.3.

3.5 Intrathecal chemotherapy

Give intrathecal methotrexate if there was lymphoma in the CSF at presentation and continued until clearance. Do not give intrathecal chemotherapy if there was only parenchymal CNS lymphoma.

3.6 Patients not considered fit for high dose methotrexate-based therapy

Note that there is a lack of good data to guide management and decisions should be based on performance status, comorbidity, risks of neurotoxicity, quality of life, life expectancy and the patient's wishes. Options are:

- WBRT
- Lenalidomide and rituximab
- Procarbazine, lomustine, vincristine (PCV)
- Single agent temozolamide (+/- rituximab), procarbazine or carmustine
- Palliative steroids

4.0 Primary Intraocular lymphoma

4.1 Note that primary intraocular lymphoma is regarded as a variant of PCNSL and the two often co-exist. Pretreatment evaluation should be as for PCNSL.

4.2 Patients eligible for induction with intensive combination chemo-immunotherapy incorporating high-dose methotrexate e.g MATRIX, MARTA

- Induction with a high dose methotrexate-based regimen should be given as for PCNSL.
- If patients have at least stable disease following induction, consolidation should be treated with either:

  ASCT-conditioned with high dose thiotepa-based chemotherapy or

  Bilateral orbital RT up to 36Gy and consider also WBRT also after considering the potential for neurotoxicity.

4.3 Patient who are unfit for systemic therapy

In the presence of isolated intraocular lymphoma options are:

- intravitreal methotrexate injections.
- Bilateral orbital RT

5.0 Relapsed and refractory PNCSL

5.1 Pre-treatment evaluation

- Re-biopsy should be attempted in patients relapsing more than two years after completing first line therapy or if there are atypical appearances on MRI brain scan
- Evaluation should be as for newly diagnosed PCNSL.

5.2 Patients fit for intensive therapy

- If the duration of first remission following high dose methotrexate was over two years consider re-treatment with high dose methotrexate-based chemotherapy.
- Otherwise treat with an ifosfamide-based regimen e.g R-ICE, R-IE, R-DeVIC.
- If not transplanted in first response and if there is at least stable disease following induction, consider consolidation with ASCT conditioned with a thiotepa-based conditioning.
- If ineligible for ASCT and WBRT naïve consider WBRT with 23.4 -36Gy.

5.3 Patients ineligible for intensive treatment

Options are:

- WBRT
- Lenalidomide and rituximab
- Procarbazine, lomustine, vincristine (PCV)

- Single agent temozolamide (+/- rituximab), procarbazine or carmustine
- Palliative steroids alone
- Supportive and palliative care

6.0 Follow up

Follow up MRI brain scans should be performed every three months for the first two years after completing treatment if the patient might be eligible for second line therapies, then every six months until five years.

Appendix

Prognostic score of untreated PCNSL (Ferreri et al, J Clin Oncol 2003)

Factors significantly and independently associated with overall survival:

- Age >60 years, raised LDH, raised CSF protein concentration *, involvement of deep regions of the brain i.e peri-ventricular, basal ganglia, brain stem, cerebellum
- Score one point for each factor if present

*the study used a cut off of > 0.45g/l in patients < 60 years > 0.6g/l in patients > 60 years

Score	0-1	1-2	3-4
All patients	80%	48%	15%
Treated with HD MTX	85%	57%	24%

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