Lymphoma Network of New Zealand

Primary CNS Lymphoma Protocol

Primary CNS lymphoma (PCNSL) is an aggressive lymphoma arising exclusively in the CNS, that is, the brain parenchyma, spinal cord, eyes, cranial nerves, and/or meninges. 95% of PCNSLs are diffuse large B-cell lymphomas (DLBCL). Other lymphoma categories like T cell lymphoma, Hodgkin's and B cell lymphomas including Burkitts, lymphoblastic, marginal zone, Waldenstroms, and small lymphocytic lymphoma are uncommon differential diagnoses. T-cell PCNSLs are ~2% of cases in Western Countries.

PCNSL is a stage 1E extranodal lymphoma that arises from the brain, eye, meninges or spinal cord in the absence of systemic disease.

Epidemiology
The median age at diagnosis is 65 and PCNSL is slightly more common among males. PCNSL accounted for approximately 2.1% of total and 6.2% of malignant primary CNS tumours diagnosed each year.

Pathology
Histologically, primary CNS DLBCL is composed of centroblasts or immunoblasts typically clustered in the perivascular space, with reactive small lymphocytes, macrophages and activated microglial cells intermixed with the tumour cells. Most tumours express pan-B-cell markers including CD19, CD20, CD22 and CD79a. PCNSL harbours chromosomal translocations of the *BCL6* gene, deletions in 6q, and aberrant somatic hypermutation in proto-oncogenes including *MYC* and *PAX5*. Inactivation of *CDKN2A* is also commonly observed in both entities. The ABC subclass accounted for > 95% of primary CNS DLBCL cases in one series *(Camilleri-Broet S, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. Blood 2006 Jan 1;107(1):190-196).*

Clinical Presentation
In 248 immunocompetent patients, 43% had neuropsychiatric signs, 33% had symptoms of increased intracranial pressure, 14% had seizures, and 4% had ocular symptoms(10). Seizures are less common than with other types of brain tumours. Unlike patients with systemic NHL, PCNSL patients rarely manifest B symptoms such as weight loss, fevers or night sweats *(Bataille B, et al. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg 2000 Feb;92(2):261-266).*

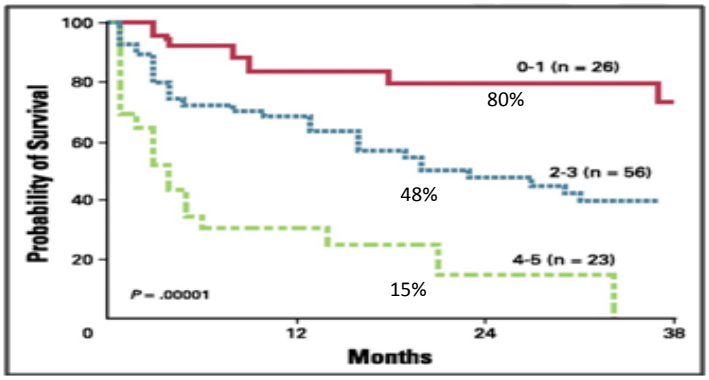
Diagnostic Criteria
The International PCNSL Collaborative Group (IPCG) has developed guidelines to determine extent of disease. A gadolinium-enhanced brain magnetic resonance imaging (MRI) scan is the most sensitive radiographic study for the detection of PCNSL. The diagnosis of PCNSL is typically made by stereotactic brain biopsy. Occasionally, if a brain biopsy cannot be performed the diagnosis can be made by cerebrospinal fluid (CSF) analysis, or by analysis of vitreous fluid aspirate in patients with ocular involvement. Concurrent leptomeningeal and ocular involvement occurs in approximately 15-20% and 5-25% of PCNSL patients, respectively. A thorough diagnostic evaluation is needed to

establish the extent of the lymphoma and to confirm localization to the CNS. Physical examination should consist of lymph node examination, a testicular examination in men, and a comprehensive neurological examination. A lumbar puncture should be performed if not contraindicated, and CSF should be assessed by flow cytometry, cytology, and/or immunoglobulin heavy-chain gene rearrangement. Because extra-neural disease must be excluded to establish a diagnosis of *primary* CNS lymphoma, CT or CT/PET scans of the chest, abdomen and pelvis, and a bone marrow aspirate and biopsy are advised to exclude occult systemic disease. Involvement of the optic nerve, retina or vitreous humor should be excluded with a comprehensive eye evaluation by an ophthalmologist that includes a slit-lamp examination. Blood tests should include a complete blood count, a basic metabolic panel, serum lactate dehydrogenase and HIV serology (*Abrey LE, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005 Aug 1;23(22):5034-5043).*

Prognostic factors (IELSG)

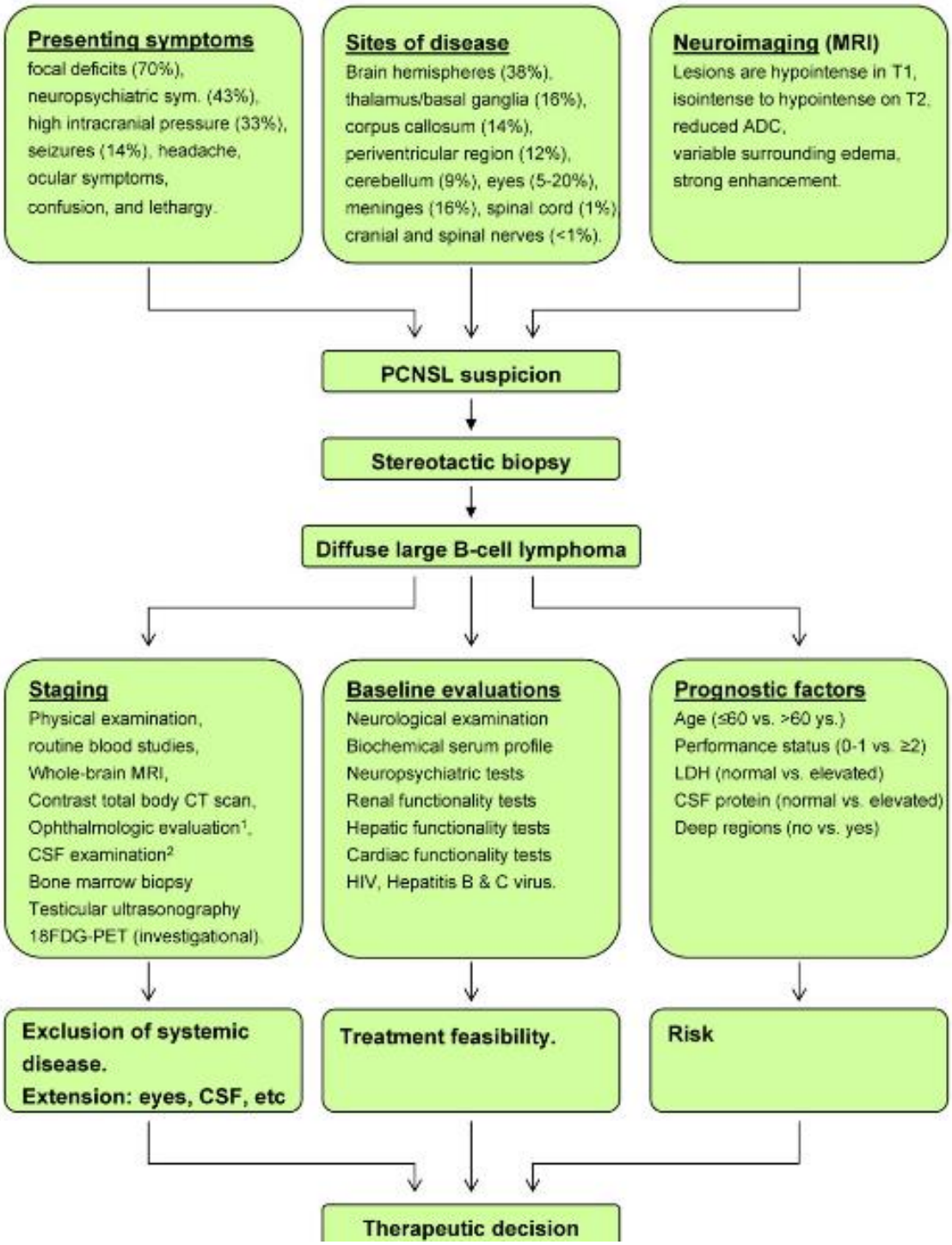
- Age >60yrs
- ECOG PS >1
- Raised LDH
- Raised CSF protein
- Deep brain sites involved (periventricular regions, basal ganglia, brainstem, and/or cerebellum)

IELSG Score



Patients with 0 to 1, 2 to 3, or 4 to 5 of these adverse risk factors had 2-year overall survival rates of 80%, 48%, or 15%, respectively. *Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003;21(2): 266-272.*

Alternatively, use MSKCC score (Appendix 2) if CSF protein level not readily available.



Andrés J. M. Ferreri Blood 2011;118:510-522

Treatment (Induction / Consolidation)

- In view of the rarity of the disease there are few randomised studies' data. There is no general consensus on optimal management of this condition, but it is agreed on that high dose methotrexate of 3g/m2 and more is the corner stone in the treatment of PCNSL. Various strategies have been employed in studies. Taking these studies together, the following considerations should be followed:
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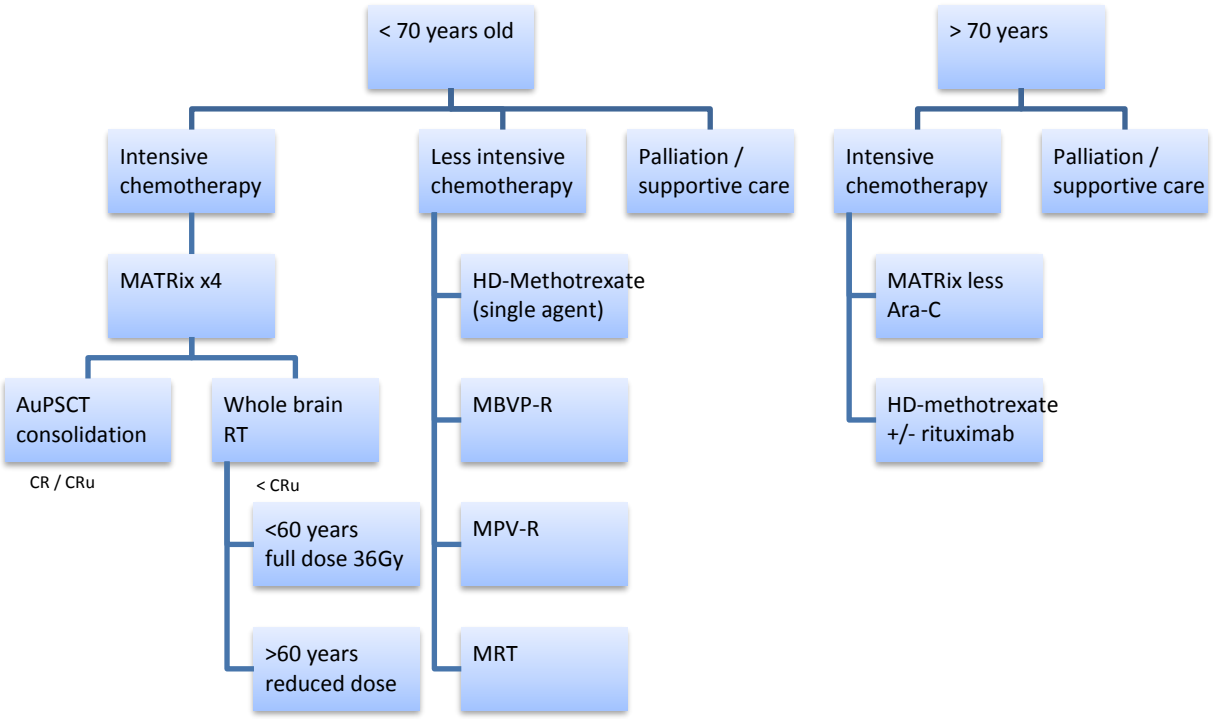
- Surgical debulking
    - Advise **against** surgical resection because it can induce neurologic deficits and treatment delays and has not been associated with survival benefits according to a meta-analysis of 50 published prospective and retrospective series
    - Tumour resection should be reserved for the timely control of neurologic deterioration because of brain herniation or ventricle dilation to provide prompt treatment in "fit" patients
    - Potentially used for those with very bulk superficial disease and imminent conning

- Steroids
    - Withheld in patients with a presumptive diagnosis of PCNSL until tissue is obtained
    - Steroid administration during anti-lymphoma therapy should be modified according to clinical requirements and until radiologic confirmation of response, and then tapered as soon as possible to reduce their immunosuppressive effect

- Radiotherapy as induction
    - In one study, radiotherapy (36-40 Gy) yielded an overall response rate of 90% but a median overall survival of only 11.6 months, with >60% of patients experiencing progression of lymphoma within the irradiated field
    - Significant long-term neurotoxicity of whole-brain radiotherapy (see neurocognitive sequelae below)
    - Whole brain radiotherapy 40gy not recommended in induction

Treatment Options for PCNSL



MATRix

FOUR (21-day) cycles

- Day -5 and 0: Rituximab 375mg/m2
- Day 1: Methotrexate 3.5g/m2 (0.5g/m2 in 15 min, followed by 3g/m2 in a 3h infusion)
- Day 2 and 3: Cytarabine 2g/m2 (1h infusion) q12h (4 doses)
- Day 4: Thiotepa 30mg/m2 (30 min infusion)

Dexamethasone can be used, but dose reduced or interrupted once tumour regression was confirmed by neurological improvement or neuroimaging.

Ferreri, A. J., Cwynarski, K., Pulczynski, E., Ponzoni, M., Deckert, M., Politi, L. S., ... & Ambrosetti, A. (2016). Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. The Lancet Haematology, 3(5), e217-e227.

Each thiotepa 15mg vial costs approximate $425 per vial excluding GST. Assuming average BSA of 2, each dose (30mg/m2) will cost approximately $1700 and 4 doses will cost $6800.

MPV-R & rd WBRT Protocol (MSKCC)

FIVE 14-day cycles of induction chemotherapy with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) given as follows:

- Day 1: rituximab 500 mg/m2
- Day 2: methotrexate 3.5 g/m2 (over 2 hours), vincristine 1.4 mg/m2 (cap at 2.8 mg))
- Days 1 to 7: procarbazine 100 mg/m2/d (odd cycles only)
- Day 3: calcium folinate rescue until methotrexate levels <0.05 micromol/L

No methotrexate dose adjustment according to creatinine clearance.

Patients who achieved a CR after five cycles received rd WBRT (23.40 Gy in 1.8-Gy fractions13) 3 to 5 weeks after chemotherapy completion

TWO (28-day) cycles of high dose cytarabine consolidation after RT

- Day 1 and 2: Cytarabine 3g/m2/day

Patrick G. Morris, et al, Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome, J Clin Oncol 31:3971-3979.

Single Agent High Dose Methotrexate with or without Rituximab

6-8cycles (14 days)

- Day 1: Methotrexate 8g/m2 IV over 4 hours
- Day 2: Calcium folinate 100mg/m2 every 6 hours until MTX < 0.05
- Day 3: Rituximab 375mg/m2 IV cycles 1 to 6

If CR, Cru → Consolidation

- Days 1-2: Cytarabine 2g/m2 over 2 hours every 12 hours x 4 doses

Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol. 2003;21(6): 1044-1049.

Methotrexate + Cytarabine (IELSG 20)

4 (21-day) cycles

- Day 1: Methotrexate 3.5g/m2
- Day 2 and 3: Cytarabine 2g/m2 q12h (4 doses)

Ferreri, A. J., Reni, M., Foppoli, M., Martelli, M., Pangalis, G. A., Frezzato, M., ... & Rossi, G. (2009). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. The Lancet, 374(9700), 1512-1520.

Other induction protocols that include agents not currently funded by Pharmac:

MBVP-R

TWO (28-day) cycles

- Day 1 and 15: methotrexate 3g/m2 + calcium folinate rescue
- Days 2 and 3: teniposide* 100mg/m2
- Day 4: carmustine 100 mg/m2
- Days 1 to 5: methylprednisolone 60 mg/m2 or oral prednisone 60mg/m2 daily
- Days 1, 7, 15 and 22 cycle #1 and Days 1 & 15 cycle #2: Rituximab 375mg/m2
- Day 5: Filgrastim sc daily until ANC > 1.0

* Note that teniposide is not currently funded by Pharmac (2017).

Poortmans, P. M., Kluin-Nelemans, H. C., Haaxma-Reiche, H., Van't Veer, M., Hansen, M., Soubeyran, P., ... & Van Imhoff, G. (2003). High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non–AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. Journal of Clinical Oncology, 21(24), 4483-4488.

MTR

Remission Induction Therapy, four (14-day) cycles

- Day 1: Methotrexate 8g/m2 IV over 4 hours
- Day 2: Calcium folinate 100mg/m2 every 6 hours until MTX < 0.05
- Day 3: Rituximab 375mg/m2 IV cycles 1 to 6
- Day 7-11: Temozolomide* 150mg/m2 PO (odd cycles only)

If CR, Cru → Consolidation

- Days 1-4: Etoposide 40mg/kg continuous IV over 96 hours

- Corrected body weight (kg) = ideal weight + 0.25 (actual weight – ideal weight)
- Days 1-4: Cytarabine 2g/m2 over 2 hours every 12 hours x 8 doses

If PR, SD, PD → off protocol

* Note that temozolomide is not currently funded by Pharmac (2017).

Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. July 2013

Consolidation with autologous peripheral stem cell transplantation protocol

HCT-ASCT

- Day 1: Rituximab 375mg/m2
- Day 2: Carmustine 400mg/m2
- Day 3 to 4: Thiotepa 5mg/kg
- Day 7: ASCT

Thiotepa comes in 100mg vial which costs 2325.24 per vial. Assuming average weight of 70kg, it will cost 32553.36 per 20mg/kg dose.

Intrathecal Treatment in PCNSL

Retrospective analysis of PCNSL outcomes at MSKCC showed that elimination of intrathecal methotrexate from induction therapy did not affect outcome in patients treated with HD-MTX at a target dose of 3.5 g/m2. This and other observations suggest that HD-MTX is sufficient to treat brain and leptomeningeal disease *(Khan RB, Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? J Neurooncol. 2002;58(2):175-178).* The event CSF disease persists following 2 cycles of induction chemotherapy treatment then IT treatment can be started as per protocol, appendix 2.

Multiple PCNSL Regimens and their RR/ PFS & OS rates

Table 1. Response rate, progression-free survival and overall survival to different treatment regimens for primary central nervous system (CNS) lymphoma.

Study	Number of Patients	Regimen	Response Rate (%) (CR and PR)	Median PFS (mo)	Median OS (mo)
Radiotherapy alone					
Nelson et al 1992[12]	41	40 Gy WBRT with 20 Gy boost	NA*	NA	12.2
Chemoradiotherapy					
Abrey et al 2000[1]	52	MPV (MTX 3.5g/m^2), cytarabine (3 gm^2) IT MTX ± 45 Gy WBRT	94	NA	60
Ferreri et al 2001[17]	13	MPV (MTX 3 g/m^2) + 36-45 Gy WBRT with boost	92	NA	25+
DeAngelis et al 2002[14]	102	MPV (MTX 2.5 g/m^2) + IT MTX + 36-45 Gy WBRT	94	24	36.9
Poortmans et al 2003[18]	52	MTX (3 g/m^2)/teniposide/carmustine + IT MTX + IT cytarabine + 30 Gy WBRT with 10 Gy boost	81	NA	46
Omuro et al 2005[16]	17	MTX (1 g/m^2)/thiotepa/procarbazine + IT MTX + 41.4 Gy WBRT with 14.4 Gy boost	88	18	32
Multidrug chemotherapy without radiotherapy					
Abrey et al 2000[1]†	22	MPV (MTX 3.5 g/m^2), cytarabine (3 g/m^2), IT MTX	NA	NA	33
Pels et al 2003 [23]	65	MTX (5 g/m^2) + cytarabine (3 g/m^2) + ifosfamide/vinca-alkaloids/cyclophosphamide + IT MTX + IT cytarabine	71	21	50
Hoang-Xuan et al 2003[22]†	50	MTX (1 g/m^2) + lomustine/procarbazine + IT MTX + IT cytarabine	71	21	50
MTX single agent					
Batchelor et al 2003[24]	25	MTX (8 g/m^2)	74	12.8	22.8+
Herrlinger et al 2002, 2005[25,26]	37	MTX (8 g/m2)	35.1	10	25

Abbreviations: PFS, progression-free survival; OS, overall survival; IT, intra-thecal; MPV, methotrexate, procarbazine, vincristine; MTX, methotrexate; NA, not available; PFS, progression-free survival; WBRT, whole-brain radiotherapy.
*After excluding patients with disease progression during radiotherapy, 26 patients were assessed by CT: 62% had a complete response (CR), 19% an almost CR and 19% a partial response.
†patients over age 60

Relapsed / Refractory PCNSL

There is no consensus on the best treatment in the relapse setting. Enrolling a patient into a clinical trial is available, otherwise, consider palliative approaches to treatment.

In patients <70years old and with good performance status and who have not had an APSCT, salvage chemotherapy with or without thiotepa can be used followed by APSCT (as above).

Salvage Regimens

- *CYVE* - TWO (28-day) cycles of high dose cytarabine and etoposide
  - Days 1 to 4: Cytarabine 2g/m2/day (3 hour infusion)
  - Days 1 to 4: Etoposide 200mg/m2/day (2 hour infusion)

  If over 60 years of age,
  - Days 1 to 3: Cytarabine 2g/m2/day (3 hour infusion)
  - Days 1 to 4: Etoposide 150mg/m2/day (2 hour infusion)

  PBSC harvested after first course of CYVE, with subcutaneous filgrastim 5mcg/kg/day starting 48 hours after end of chemotherapy.

  Transplant intensive chemotherapy is as per protocol

How, J., Warner, M., Shustik, C., & Laneuville, P. (2010). Cytarabine and Etoposide (CYVE) as First-Line Therapy for Primary Central Nervous System Lymphoma. Blood, 116(21), 4895-4895.

- *Illerhaus protocol (*Induction: 2 cycles)
  - Day 1: Rituximab 375mg/m2
  - Day 2-3: Cytarabine 3g/m2
  - Day 3: Thiotepa 40mg/m2

HCT-ASCT

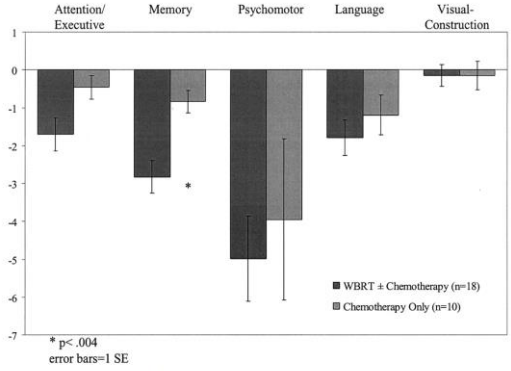
- Day 1: Rituximab 375mg/m2
- Day 2: Carmustine 400mg/m2
- Day 3-4: Thiotepa 5mg/m2
- Day 7: ASCT

Illerhaus, G., Fritsch, K., Schmidt-Wolf, I., Schroers, R., Egerer, G., Korfel, A., ... & Stilgenbauer, S. (2014). High Dose-Chemotherapy Followed By Autologous Peripheral Blood Stem Cell Transplantation for Patients with Refractory or Recurrent Primary Central Nervous System Lymphoma–Results of a Multicenter Study By the Germany Collaborative PCNSL Study Group. Blood, 124(21), 2527-2527.

Neurocognitive Sequelae of chemo radiotherapy in PCNSL

Neurocognitive effects are common and are multifactorial:

a. CNS lymphoma – whilst imaging shows solitary lesions, autopsy studies have shown widespread infiltrative disease.
b. Age-related co-morbidities can be common in this age group (median age for PCNSL 60yrs).
c. Treatment related – both methotrexate and WBRT+/- chemotherapy have neurological sequelae. However, the effects are more pronounced with whole brain radiotherapy especially in those >60yrs of age.



Correa, D. D. et al. Neurology 2004;62:548-555

The cumulative incidence of neurotoxicity at five years has been reported at 24% but is higher in those >60years of age and in those treated with WBRT.

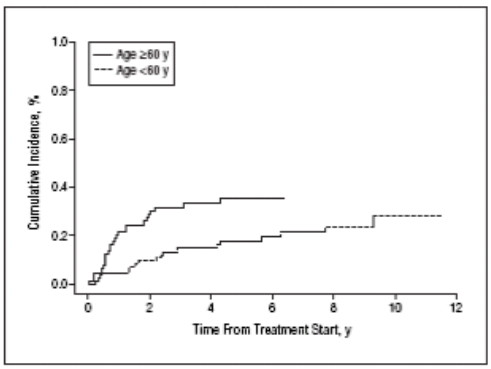


Figure 2. The incidence of neurotoxicity stratified by age, showing that although older patients are at a significantly higher risk, the development of neurotoxicity is also a concern in long-term survivors younger than 60 years.

Neurotoxicity is progressive with all patients eventually requiring nursing care and the majority dying from causes related to neurotoxicity. The onset is variable and increases with time but occurs in some within months of therapy. The pattern of neurocognitive effects is of a subcortical dementia characterised by psychomotor slowing, executive and memory dysfunction, behavioural changes, gait ataxia and incontinence. The cognitive dysfunction occurs early and is followed by motor and eventually autonomic dysfunction. Imaging studies show diffuse white matter disease and cortical/subcortical atrophy.

Follow up:

Once in remission, 3 monthly follow up with MRI brain for first 2 years, 6 monthly for 3 years then yearly afterwards. *(Langner-Lemercier et al, Neuro-Oncology* 18(9), 1297–1303, 2016)

Appendix 1

MSKCC score

- Class 1: age younger than 50
- Class 2: age older than 50 and Karnofsky performance score (KPS) higher than 70
- Class 3: age older than 50 and KPS less than 70.

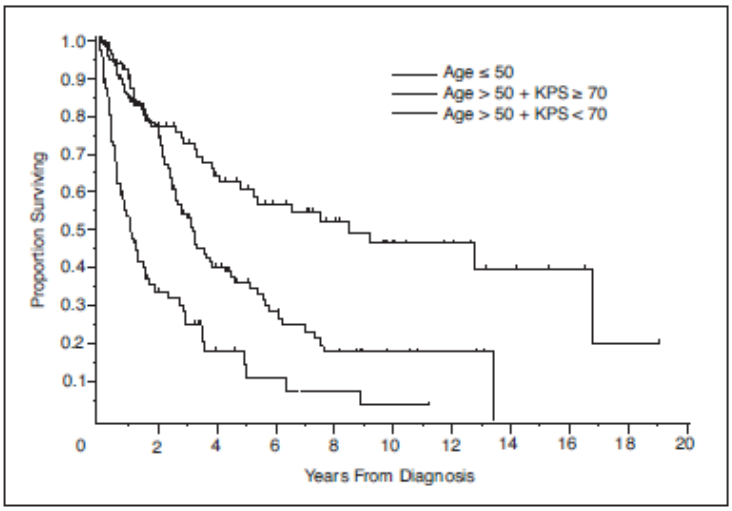


Fig 1. Kaplan-Meier curve showing overall survival of the 282 Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) primary CNS lymphoma patients stratified by recursive partitioning analysis classification. Age younger than 50, class 1; age older than 50 and Karnofsky performance score (KPS) higher than 70, class 2; age older than 50 and KPS less than 70, class 3.

http://ascopubs.org/doi/full/10.1200/jco.2006.08.2941

Appendix 2.

Intrathecal treatment regimen

Agent	Dose / day	Route	Day
Methotrexate	15 mg OR 10 mg	Intrathecal (via LP) intraventricular	twice a week until 2 x negative CSF then tapering*
Dexamethasone OR Methylprednisolone	4 mg 25 mg	Intrathecal or intraventricular	twice a week until 2 x negative CSF then tapering*

* after 2 x negative CSF treat once a week for 2 times, then once every 14 days 2 times and once every 4 weeks two times or until start of WBRT, whichever comes first.

Intrathecal/intraventricular treatment should be avoided on the days the HD-Ara-C is administered.

In case of persistent disease after 4 intrathecal or intraventricular administrations switch to cytarabine 70 mg in combination with dexamethasone or methylprednisolone administered intrathecally.

NO further intrathecal or intraventricular treatment after commencement of WBRT.