Primary CNS Lymphoma

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare subtype of non-Hodgkin's lymphoma in which disease is restricted to the craniospinal axis [1]. Ocular involvement can occur in 10-20% of cases and leptomeningeal disease is documented in 20-30%. PCNSL represents 2% of all lymphoma diagnoses (and 3% of all brain tumour presentations) and the incidence is reported in the range of 4 cases/million person-years. The only known risk factor for PCNSL development is congenital or acquired immunodeficiency. In the recent era of highly active antiretroviral therapy use, a dramatic reduction in incidence of immunodeficiency-associated PCNSL has occurred, correlating with a decline in the proportion of HIV-infected individuals with CD4+ cell counts less than 50/mm^3 [2]. The majority of this document will focus on the management of PCNSL in immunocompetent individuals with a brief discussion of HIV-associated PCNSL. A practice guideline on the management of PCNSL has been published by the British Committee for Standards in Haematology (BCSH) **www.bcshguidelines.com** [3]. The Odette Cancer Centre Hematology Site Group endorses this document.

Diagnosis

Unlike individuals with systemic non-Hodgkin's lymphoma, patients with PCNSL classically present with focal neurologic or cognitive deficits. Focal findings are present in >50-70% of all patients. Altered mental states (memory loss, confusion, etc.) and headache complaints are each noted in approximately 1/3 of patients. New onset seizure is less common (<10%). The classic radiologic picture is of a solitary non-hemorrhagic lesion in the deep white matter with periventricular localization. On MRI, the lesions tend to be isointense to hypointense on T2-weighted images with dense enhancement following gadolinium administration. The diagnosis of PCNSL is dependent on an adequate biopsy specimen with immunohistochemistry. Stereotactic needle biopsy is preferred. If ocular or leptomeningeal disease is suspected, a vitrectomy or CSF cytology studies may establish the tissue diagnosis. The majority (>90%) of biopsies demonstrate diffuse large B-cell histology, with Burkitt's lymphoma, indolent B-cell lymphomas, and T-cell histologies rarely reported [4].

Baseline Investigations

The following investigations are indicated for most patients with PCNSL [5]:

- Comprehensive physical examination (including testicular examination in men)
- Comprehensive neurologic examination (including MMSE) – **see page 7**
- CBC, differential, blood film
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH
- HIV serology
- Gadolinium-enhanced MRI brain
- CT chest, abdomen, pelvis
- Unilateral bone marrow biopsy
- Ophthalmology consultation (including slit-lamp examination)

Patients who will be managed with palliative intent may have more limited staging investigations with a focus on identification of disease that is likely to require symptomatic management.

CSF Analysis

A lumbar puncture to evaluate leptomeningeal involvement should be completed and can be accompanied by the initial dose of intrathecal chemotherapy. The following studies should be sent:

- Cell count
- Glucose and protein
- Cytology
- Flow cytometry
- PCR for immunoglobulin H gene rearrangement

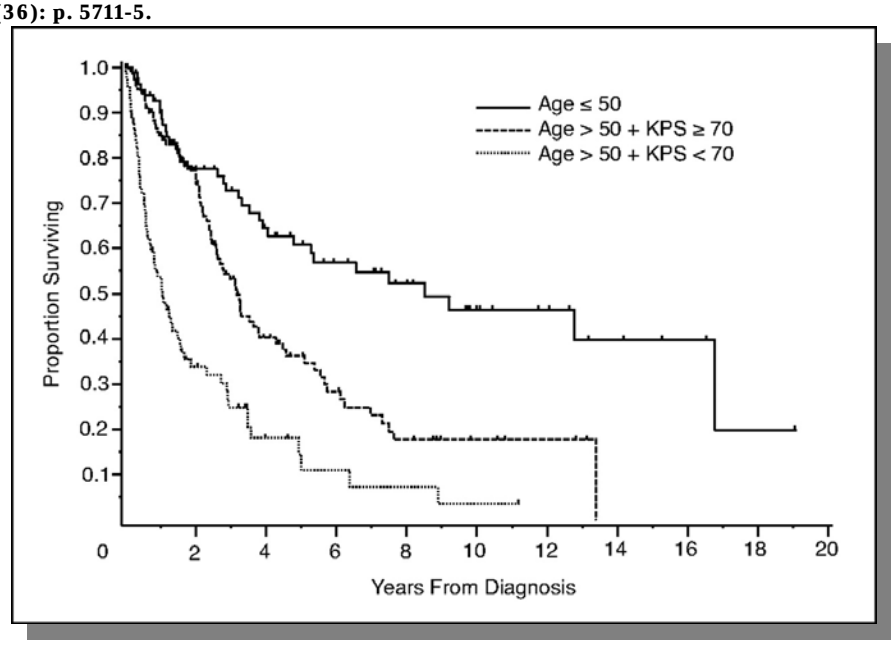
Staging & Prognosis

The International Extranodal Lymphoma Study Group has noted that several factors are associated with a poor prognosis in PCNSL. Age older than 60 years, ECOG performance status greater than 1, elevated LDH, high CSF protein concentration, and deep brain involvement (including periventricular, basal ganglia, brainstem, and/or cerebellar disease) were independently predictive for poor survival. Patients with 0-1, 2-3, or 4-5 adverse factors had a 2-year overall survival of 80%, 48%, or 15%, respectively [6]. A more recent staging system has been developed and validated by the Memorial Sloan Kettering (MSKCC) Group [7]. The group studied multiple factors in over 300 patients and found only two factors, age and performance status, were predictive of outcome. These factors were able to differentiate patients into three very different prognostic groups. Patients with Class I prognosis (age under 50) experienced a median overall survival of 8.5 years whereas patients who were Class III (age over 50 and poor functional status).

Stage Definition

	Definitions	Patients	Med OS (yrs)
Class I	Age <50	30%	8.5
Class II	≥50 and KPS ≥70	44%	3.2
Class III	≥50 and KPS <70	26%	1.1

*KPS = Karnofsky performance score. Note that a KPS score of 70-80 is equivalent to an ECOG score of 1. A KPS score of 60-70 is equivalent to an ECOG score of 2. This prognostic model was derived from data from a large single-institution (representing 338 consecutive patients) and externally validated on a large intergroup clinical trial data set (representing n=194 patients).



Therapy for PCNSL

The historical mainstay of therapy in PCNSL was previously whole-brain radiation therapy (WBRT) alone. A regimen studied by the Radiation Therapy Oncology Group (RTOG) consisted of 40Gy to the whole brain and a 20Gy boost to gross tumor [8]. Although the tumors appeared highly responsive to radiation (with overall response rate ORR 90%), relapse was inevitable and long-term median survival was less than 12 months. Moreover, WBRT is associated with the development of delayed neurotoxicity, a progressive subcortical dementia characterized by a triad of memory impairment/behavioral changes, gait ataxia, and urinary incontinence [9]. The risk is thought to be highest in patients older than 60 [1].

Because of the limited long-term efficacy of WBRT alone, there has been considerable interest in combining chemotherapy with radiation to improve response and survival. CHOP-based chemotherapies have been studied, but have not offered additional survival benefit to radiation used alone, presumably because of the lack of penetration to the CNS sanctuary sites when the blood-brain barrier is intact [10]. Research has centered on the role of systemic methotrexate at doses known to penetrate into the CNS preceding WBRT. Initial phase II outcomes demonstrated significant improvements in response and long-term disease control compared to historical controls [11-13].

This research culminated in a RTOG multi-centre phase II study of 98 patients with PCNSL. The group adopted the MSKCC "DeAngelis" protocol which included five cycles of methotrexate (2.5 g/m^2), vincristine, and oral procarbazine (MVP) with intrathecal methotrexate preceding WBRT (45Gy) and post-WBRT high-dose cytarabine [14]. In this study, ORR reached 94% including 58% complete responses and the median progression-free survival was 25 months (with median overall survival 37 months). Neurotoxicity was reported in 15% of patients, although the duration of follow-up may not have been extensive enough to define a relatively late outcome.

Recently, MSKCC reported long-term follow-up (almost 10 years) of their experience with the combined-modality therapy (CMT) approach [15]. Median overall survival was 51 months for the entire cohort of 57 patients. In patients under 60, median progression-free survival and overall survival had not been reached after 115 months of follow-up and neurotoxicity had occurred in 26% of patients. In patients 60 and over, progression-free survival had not been reached but the median overall survival was only 29 months. The increased mortality appeared to be associated with increased neurotoxicity, which occurred in 75% of patients. Another subset of patients in this report (predominantly over 60) had deferred radiation and only received chemotherapy. In this subgroup, median overall survival was again only 29 months. In this group, progression-free survival was only 7 months, suggesting that mortality when only chemotherapy is given is driven by a high-risk of CNS relapse. Neurotoxicity was not prominent in the patients treated with chemotherapy alone. This study highlights the excellent long-term results of CMT in younger (<60) patients. In patients 60 and over, radiation therapy is associated with improved lymphoma control but at the cost of excessive neurotoxicity (and considerable mortality) and does not appear to offer a convincing survival benefit.

The use of chemotherapy alone has been studied, in an attempt to reduce the toxicity of CMT. In one multi-centre phase II study of high-dose methotrexate (single agent 8 g/m^2) – based therapy, ORR was 74% but median progression-free survival was short (13 months) [16]. Similarly, our own experience with the MVP combination alone (with radiation deferred for relapse or progression) yielded similar long-term outcomes (median PFS of 14 months and OS of 41 months) [17, 18]. Neurotoxicity was not a prominent concern in either of these studies. Thus, although long-term toxicity is improved when radiation is omitted, early relapse of PCNSL is of concern.

The optimal methotrexate-based regimen is unclear in the literature. In a retrospective analysis of 378 international patients with PCNSL, treatment with high-dose methotrexate in combinations with other cytostatic agents resulted in improved outcomes (survival) compared to use of the agent alone [19]. The use of high-dose cytarabine with methotrexate was in particular more effective than the combination of methotrexate and alkylating agents ($p=0.005$). Cytarabine was generally given concurrently with methotrexate in a variety of dose intensities and schedules.

Recommendations:

- Patients who under the age of 60 should be offered CMT (High-dose methotrexate-based chemotherapy followed by WBRT). Such patients should be seen in consultation by a radiation oncologist early in the course in order to discuss the relative risks and benefits of radiotherapy. Select patients may not accept the risk of neurotoxicity and may elect to be treated with combination chemotherapy alone.

- Patients who are 60 and older should receive high-dose methotrexate-based chemotherapy alone (MVP).

- High-dose methotrexate should be offered as part of a multi-agent chemotherapy combination. The choice of regimen is dependent on local familiarity and comfort with the combinations and necessary monitoring. At the Odette Cancer Centre, we support the use of the MVP regimen (for 5 cycles).

Management of Relapsed Disease

Palliative WBRT can be considered for individuals with relapsed/refractory PCNSL who did not receive radiation as part of their initial therapy. In a study of 27 patients who relapsed following high-dose methotrexate-based therapy, WBRT was associated with a response rate of 75% and median overall survival was 11 months from the start of radiotherapy [20].

Dexamethasone can be initiated for short-term palliation [3]. Other salvage options include repeated use of high-dose methotrexate. In one report, response rates of 91% were attained and extended remissions were documented in patients previously achieving a complete response to their prior therapy [21]. High-dose cytarabine can also cross the blood-brain barrier and offers a non-cross resistant alternative to repeated methotrexate [22].

Temozolomide provides a tolerable oral alternative to the above options. Responses are found in approximately one-quarter of patients and remissions are brief [23]. Other salvage regimens studied include temozolomide with rituximab, combination procarbazine, lomustine, and vincristine, and topotecan [1].

High-dose therapy and autologous stem cell transplantation has been studied as a salvage approach in PCNSL [24]. In one study of 22 patients who were chemosensitive to salvage cytarabine and etoposide, high-dose therapy (thiotepa, busulfan, and cyclophosphamide) and stem-cell rescue resulted in an overall survival probability of 64% at 3 years. This approach remains experimental.

A suggested approach to salvage of relapsed PCNSL is as follows:

- Patients who have previously received MTX-based chemotherapy alone and achieved a long initial response duration (>24 months) should receive high-dose MTX again (3.5 g/m^2 for 4 cycles)
- Patients who have previously received MTX-based chemotherapy alone but attained a short duration of response should be considered for WBRT.
- Patients who have previously received MTX-based chemotherapy and WBRT should be treated with high-dose cytarabine (2 g/m^2 q12h for two doses/cycle x 4 cycles).

Special Considerations

Intrathecal Chemotherapy

The additional benefit of intrathecal (IT) chemotherapy when added to high-dose methotrexate is unclear. In a retrospective case-control study from the MSKCC, patients who received IT chemotherapy as part of an institutional policy prior to 1995 were matched to those who did not receive IT treatment after the policy changed (following 1995) [25]. No difference was noted in CSF relapse rate, event-free survival, or overall survival with the use of IT chemotherapy. In another retrospective review of 378 internationally treated patients, the addition of IT chemotherapy again did not alter the 2-year overall survival (51% OS in IT treated

vs. 40% without IT chemotherapy, p=0.43) [19]. There is currently no evidence that is supportive for the prophylactic role of intrathecal chemotherapy when added to high-dose methotrexate-based chemotherapy [3].

Individuals with leptomeningeal disease at presentation warrant frequent dosing of IT chemotherapy until the CSF is cleared of involvement. A reasonable approach would be to instill IT chemotherapy twice weekly until the CSF is clear (or until 4 weeks), then once weekly for 4 weeks, followed by a return to the baseline IT dosing defined by the DeAngelis protocol.

Although intra-Ommaya instillation of chemotherapy is associated with more reliable delivery and intra-ventricular drug concentrations [26], there are significant risks that must be balanced. Complications include infection/meningitis (incidence 4-9%), malposition/migration (3-13%) and hemorrhage (1-3%) [27]. The decision to proceed with intrathecal vs. Ommaya based therapy should be individualized based on discussions with each patient and burden of disease. Patients with known leptomeningeal involvement likely warrant Ommaya insertion to facilitate frequent IT dosing.

Intraocular Lymphoma

Concomitant intraocular lymphoma can occur in 10-15% of patients with PCNSL [28]. Most studies specifically documenting therapy for IOL are small case series. High-dose MTX (at a dose of 8gm/m^2) can penetrate into the eye with micromolar concentrations achieved in both the aqueous and vitreous humor [29]. Pharmacokinetics for doses lower than this level, however, has not been formally studied. In one report from the IELSG, the use of chemotherapy alone appeared to result in more frequent ocular recurrences compared to a combined approach of chemotherapy with ocular radiation [28]. Concurrent intraocular and CNS lymphoma should be treated with systemic MVP followed by radiation to both globes (and possibly the brain if the patient is less than 60). Isolated intraocular disease should be treated the same way [3].

HIV-Associated PCNSL

PCNSL in immunodeficient (HIV-associated) individuals is associated with unique diagnostic, prognostic, and therapeutic issues. Historically, in the era preceding the routine use of highly active antiretroviral therapy, HIV-associated PCNSL generally presented late in the course of advanced HIV/AIDS (CD4 counts <50/mm^3) and carried a poor prognosis [2]. Patients were generally managed palliatively with WBRT and concomitant steroids (with initiation of HAART). Median survival was rarely beyond several months in duration [30]. In the current HAART era, the potential to treat patients with similar high-dose methotrexate-based regimens has been studied, and should be considered in patients with adequate HIV control (on HAART) [31].

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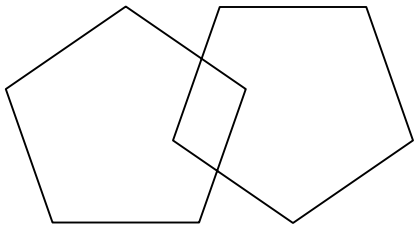
The Mini-Mental State Exam

Patient: _____ Examiner: _____ Date: _____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3 Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serials 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No, ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. Journal of Psychiatric Research, 12(3): 189-198, 1975. Used by permission.