Primary Central Nervous System Lymphoma: Saudi Lymphoma Group's Clinical Practice Guidelines for Diagnosis, Management and Follow-up

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Received: 25-03-2019 **Revised:** 06-05-2019 **Accepted:** 24-07-2019 **Published:** 28-08-2019

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare variant of the aggressive extranodal non-Hodgkin lymphoma of the diffuse large B-cell type. It accounts for about 1% of all lymphomas, 4%–6% of all extranodal lymphomas and 3% of all central nervous system (CNS) tumors.[1] The risk of developing PCNSL is highly associated with having congenital or acquired immunodeficiencies such as human immunodeficiency virus (HIV) infection. The incidence is highest in patients aged >65 years, who represent the largest proportion of immunocompetent patients.[2-4] Few population studies about PCNSL have been published in Saudi Arabia; however, recent studies have shown a slight female predominance, and the mean age at diagnosis has been found to be 50.4 years (range: 20 to ≥60 years).[5,6]

METHODS

A committee comprising experts in hematology and medical oncology was established under the supervision of the Saudi Lymphoma Group and in collaboration with the Saudi Oncology Society. For collecting evidence, a literature search was carried out with relevant keywords using online database search engines such as PubMed/Medline, Web of Science and Scopus. In addition, an expert's opinion was considered when necessary. The levels of evidence used in developing this guideline were as follows:

- Evidence level (EL)-1 (highest), evidence from Phase III randomized trials or meta-analyses
- EL-2 (intermediate), evidence from well-designed Phase II trials or Phase III trials with limitations
- EL-3 (low), evidence from retrospective or observational studies/reports and/or expert opinion.

This easy-to-follow grading system is convenient for readers to understand and allows an accurate assessment of the guideline's applicability in individual patients.[7]

Access this article online	
Quick Response Code:	Website: www.sjmms.net
	DOI: 10.4103/sjmms.sjmms_103_19

How to cite this article: Sagheir A, Alhejazi A, Al-Mansour M, Alhashmi H, Kandil M, Motabi I, *et al*. Primary central nervous system lymphoma: Saudi Lymphoma Group's clinical practice guidelines for diagnosis, management and follow-up. Saudi J Med Med Sci 2019;7:219-21.

1. PATHOLOGIC DIAGNOSIS

1.1. Magnetic resonance imaging (MRI) with contrast should be performed in all suspected cases of PCNSL to define the site and extent of disease
1.2. Fluid-attenuated inversion recovery and T1-weighted sequences before and after contrast injection are the methods of choice for diagnosis
1.3. The diagnosis of PNCSL should be confirmed pathologically according to the WHO classification (EL-1)[1]
1.4. Stereotactic needle brain biopsy is the optimal method to obtain a histopathological diagnosis; therefore, surgical reduction of PCNSL is not recommended (EL-3)[8]
1.5. Steroids should be withheld for at least 7–10 days prior to biopsy to minimize its lymphocytotoxic effect on histological diagnosis (EL-3)[9,10]
1.6. The immunohistochemical markers for lymphoma cell characterization should include pan-B-cell antigens (i.e., CD19, CD20, CD22 and CD79a), BCL6, MUM1/IRF4, BCL2 and CD10 (EL-1)[1,11,12]
1.7. Other histologies for CNS lymphomas include Burkitt's lymphoma, lymphoblastic, indolent lymphoma (marginal zone lymphoma and small lymphocytic lymphoma) and T-cell lymphoma.

2. DIAGNOSIS AND WORKUP

2.1. Pathology review is essential for all referral cases
2.2 Complete history should be documented (i.e., age, comorbidities, B-symptoms, Eastern Cooperative Oncology Group [ECOG] performance, neurological and neuropsychiatric symptoms, hepatitis or HIV risk factors, medications, allergy to contrast media or drugs as well as social and family history)
2.3. Physical examination should include
   a. Complete neurological examination, including the Mini-Mental State Examination (MMSE)
   b. Assessment of lymph nodes, Waldeyer's ring, spleen, liver and skin
2.4. Laboratory evaluations of all patients should include complete blood count with differential count, liver and renal function tests as well as routine blood chemistry including lactate dehydrogenase [LDH], electrolytes and calcium
2.5. Hepatitis serology tests (hepatitis B and C viruses) should be carried out
2.6. Screening test for HIV is required
2.7. Whole-brain MRI (contrast-enhanced) should be performed
2.8. Computed tomography scan of the neck and chest and abdomen and pelvis should be performed
2.9. Bone marrow biopsy is recommended for staging
2.10. Testicular ultrasonography is recommended in elderly patients
2.11. Cerebrospinal fluid (CSF) examination (lymphoma cell count, protein and glucose levels, cytology, flow cytometry and immunoglobulin heavy-chain variable region gene rearrangement studies)
2.12. To investigate ocular involvement, the slit-lamp examination should be carried out
2.13. Cardiac function (i.e., left ventricular function) should be assessed by echocardiogram before the treatment
2.14. Pregnancy test should be done for women of childbearing age
2.15. For prognosis, follow the International Prognostic Score for PCNSL:
   i. Age >60 years
   ii. Eastern Cooperative Oncology Group Performance Status (ECOG PS) >1
   iii. Elevated serum LDH
   iv. Elevated CSF protein concentration
   v. Tumor localization within the deep regions of CNS.
2.16. Based on these predictors, the risk group classifications are as follows: 0–1 (low), 2–3 (intermediate) or 4–5 (high risk) (EL-3).[13]

3. MANAGEMENT

3.1. The treatment of PCNSL is based on age and performance status[14,15]
3.2. High-dose methotrexate (HDMTX) (≥3 g/m2) is the standard induction therapy to cross the blood–brain barrier and yield cytotoxic levels in the CSF. It should be delivered over 2–4 h (rapid infusion) through at least 4–6 injections at intervals of not >2–3 weeks (EL-1)[16-18]
3.3. HDMTX infusions require pre- and posthyperhydration, urine alkalinization, leucovorin rescue and MTX concentration monitoring
3.4. HDMTX in combination with temozolomide and rituximab improves the response rates compared with HDMTX alone
3.5. High-dose consolidation of cytarabine and etoposide following HDMTX-based polychemotherapy induction therapy is recommended (EL-2)[19]
3.6. Palliative whole-brain radiotherapy should be considered for patients deemed unsuitable to receive HDMTX owing to tolerability or relapse after treatment with HDMTX and CNS-penetrating chemotherapy or being unfit for further chemotherapy (EL-3).

4. FOLLOW-UP

4.1. Every 3 months for 2 years and then once every 6 months
4.2. History and physical examination should be documented in each visit
4.3. Cognitive evaluation, such as MMSE, should be conducted in every visit
4.4. Contrast-enhanced MRI of the brain must be performed in each visit
4.5. Ophthalmologic examination and CSF analysis should be carried out when clinically indicated (EL-3).

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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