Primary Mediastinal Large B-Cell Lymphoma: Saudi Lymphoma Group's Clinical Practice Guidelines for Diagnosis, Management and Follow-up

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INTRODUCTION

Primary mediastinal large B-cell lymphoma (PMBL) is a distinct subtype of diffuse large B-cell lymphoma (DLBCL), accounting for 6%–10% of the cases. PMBL typically presents in women during the third to fourth decade of life.[1] However, its incidence in Saudi Arabia is yet unknown.

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, expert 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.[2]

1. PATHOLOGIC DIAGNOSIS

1.1. The preferred method for establishing the diagnosis of PMBL is surgical biopsy either by excision of the involved lymph node or, if not possible, by mediastinoscopy or thoracoscopy (EL-3)[3,4]

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1.2. Fine needle aspirates or core biopsies may be non-diagnostic because of inadequate sample or presence of extensive necrosis, fibrosis or crush artifacts

1.3. PMBL usually arises from the thymus. This is composed of large cells with pale cytoplasm, variable nuclear features, Reed–Sternberg-like cells and sclerosis that may raise suspicion of Hodgkin lymphoma[5-7]

1.4. The tumor cells express B-cell antigens such as CD19, CD20, CD22, CD79a and CD45 and weak CD30 in >80% of cases.[1,8,9] These cells also frequently express other markers of Reed–Sternberg cells such as IRF4/MUM1.[10] Regarding the oncogenic abnormalities, a gain in chromosome 9p24 is seen in up to 75% of the cases. Immunoglobulin genes are rearranged but *BCL-2*, *BCL-6* and *MYC* are rare or uncommon.[3,9,11]

2. DIAGNOSIS AND WORK-UP (EL-3)

2.1. Pathology review is essential for all potential cases

2.2. Evaluations should include complete history (i.e., age, gender; comorbidities; B-symptoms; Eastern Cooperative Oncology Group performance status; hepatitis or human immunodeficiency virus risk factors; medications; allergy to contrast media or drugs as well as social and family history) and physical examination (i.e., of lymph nodes, Waldeyer's ring, spleen, liver and skin)

2.3. Laboratory evaluations of all patients should include complete blood count (CBC) with differential count, liver and renal function test as well as routine blood chemistry including lactate dehydrogenase, electrolytes and calcium

2.4. Hepatitis serology tests (hepatitis B and C viruses) should be carried out

2.5. Computed tomography (CT) scan of neck and chest, abdomen and pelvis (CAP) should be performed in all cases

2.6. Bone marrow biopsy is recommended for staging

2.6. Cardiac function should be assessed by echocardiogram because pleural and pericardial effusions are common at presentation

2.7. Pregnancy test should be done for women of childbearing age

2.8. Although PET/CT is not part of the initial staging work up, it is a useful tool and surrogate test to guide the need for consolidation radiotherapy after six cycles of chemotherapy

2.9. Clinical staging should be based on the Lugano modification of Ann Arbor staging system.[12]

3. MANAGEMENT

3.1. Currently, there is no standard therapy for PMBL. In terms of radiotherapy use, there are concerns regarding its long-term toxicity, especially in young patients. Additional concerns are the optimal type and duration of chemoimmunotherapy and risk of relapse

3.2. Six cycles of CHOP-R 21 is the preferable chemotherapy for DLBCL at all stages of PMBL (EL-2)[13,14]

3.3. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) can be used for patients who wish to avoid radiation therapy, such as those aged <30 years and women with disease requiring irradiation of the breast tissue (EL-2)[15]

3.4. Management of patients with relapse is as follows:

3.4.1. Restaging is required including blood work, CT of neck and CAP as well as bone marrow biopsy

3.4.2. For all patients aged <60 years, management includes salvage chemotherapy with R-ESHAP (rituximab, etoposide, methylprednisolone, high-dose cytarabine and cisplatin) or R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin) for a maximum of three cycles followed by high-dose chemotherapy and autologous stem cell transplant (EL-2)[16,17]

3.4.3. Patients who are not transplant candidates could be treated with conventional chemotherapy, such as ESHAP and GDP, and with involved-field radiation therapy for symptomatic sites

3.4.4. Pembrolizumab can be used for patients who have relapsed after two or more prior lines of therapy (EL-3).[18]

4. FOLLOW UP (EL-3)

4.1. Every 3 months for 2 years, then every 6 months for 3 years, and then annually

4.2. History and physical examination should be documented in every visit

4.3. CBC with differential count, erythrocyte sedimentation rate and liver function test should be requested in every visit

4.4. Thyroid-stimulating hormone test should be carried out at least once annually if the patient had received radiotherapy to the neck

4.5. CT of neck and CAP is required every 6–12 months for first 2 years, and then based on the clinical presentation

4.6. Chest X-ray should be performed at each visit in the first 2 years, and then every other visit, especially for patients who previously had intrathoracic disease

4.7. Mammogram is required who received chest radiotherapy, beginning 10 years after diagnosis of lymphoma or when aged 40 years, whichever comes first

4.8. Annual influenza immunization is recommended.[19]

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Conflicts of interest

There are no conflicts of interest.

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