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

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a common cancer among Saudis, accounting for 6.9% of all newly diagnosed cancers in 2015. NHL is the second and fifth most common cancer among Saudi male and female population, respectively, with a ratio of 1.54:1. The age-standardized rate was 5.9/100,000 for males and 4.1/100,000 for females. The most common subtype of NHL is diffuse large B-cell lymphoma (DLBCL), accounting for approximately 51% of NHL among Saudi adults (240 males and 181 females).[1]

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. Excisional biopsy is the optimal method for the initial diagnosis of DLBCL. Presence of large cells, basophilic cytoplasm, vesicular nuclei

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and prominent nuclei with high mitotic rate is indicative of DLBCL (EL-3)

1.2. Fine needle aspiration (FNA) biopsy alone is not suitable for the initial diagnosis of DLBCL (EL-3)

1.2. The immunohistochemistry (IHC) panel includes CD19, CD20, CD22, CD79a, BCL-2 and Ki67+ to confirm the morphological diagnosis of DLBCL (EL-1)[3]

1.3. IHC staining for CD10, BCL-6 and MUM1 is recommended to differentiate between germinal cell center B-cell (GCB) and non-GCB cell of origin (EL-3)[4]

1.4. CD5 expression is correlated with worse prognosis, and thus its IHC staining should be done in all DLBCL cases (EL-3)[5,6]

1.5. *MYC* rearrangement is associated with poor outcome, especially when combined with *BCL-2* or *BCL-6* expression (double-or triple hit lymphoma) (EL-3)[7,8]

1.6. Analysis of *MYC* rearrangement by fluorescence *in situ* hybridization (FISH) should be done on all patients eligible for aggressive therapy as well as those with intermediate morphological features between DLBCL and Burkitt's lymphoma (EL-3)[9,10]

1.7. In all cases with *MYC* rearrangement, *BCL-2* and *BCL-6* expression should be assessed by FISH

1.8. Detection of *MYC* and *BCL-2* by IHC is not surrogate for *MYC* rearrangement; however, it is strongly recommended in all cases of DLBCL to identify patients with this dual expression, as they may benefit from a more aggressive therapy and central nervous system (CNS) prophylaxis (EL-3).[11,12]

2. DIAGNOSIS AND WORKUP

2.1. Pathology review is essential for all referral cases

2.2. Evaluations should include complete history (i.e., age, gender, comorbidities, B-symptoms, ECOG performance status, hepatitis or human immunodeficiency virus [HIV] 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, CNS, gastrointestinal tract, lung, bone and skin)

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

2.4. Hepatitis serology (hepatitis B surface antigen, core antibody and surface antibody as well as hepatitis C virus), and PCR for hepatitis B surface antigen-positive or core antibody-positive cases

2.5. Screening test for HIV is required

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

2.7. Magnetic resonance imaging (MRI) is the modality of choice in patients suspected of having a CNS lymphoma

2.8. A diagnostic lumbar puncture should be considered in high-risk patients

2.9. Bone marrow biopsy is recommended as standard for staging majority of patients with DLBCL

2.10. Positron emission tomography (PET)/CT is recommended when available (EL-3)[13,14]

2.11. Cardiac function (i.e., left ventricular function) should be assessed by echocardiogram before treatment

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

2.13. Infertility and fertility preservation should be discussed, depending on the type of treatment.

3. STAGING

3.1. Should be based on the Lugano modification of Ann Arbor staging system (EL-1).[15]

4. MANAGEMENT

4.1. Treatment of DLBCL is based on the extent of the disease.

- 4.1.1. Stages: Stages I or II versus Stages III or IV according to Ann Arbor staging system[15]
- 4.1.3. Limited stage is defined as Stages I or II, and non-bulky disease
- 4.1.4. Advanced stage is defined as Stages III or IV or bulky disease, regardless of the stage
- 4.1.2. Bulky disease: Defined as having a tumor of diameter ≥7.5 cm.

4.2. Cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab 21-day cycles (CHOP-R-21) is the standard chemotherapy for DLBCL (EL-1)[16,17]

- 4.2.1. Non-bulky, limited Stages I and II
  - 4.2.1.1. Combined modality therapy consisting of three cycles of CHOP-R 21 is the recommended treatment followed by involved-field radiation therapy (ISRT)
  - 4.2.1.2. An alternative option is the PET-adapted

approach, where PET/CT is done after three cycles of CHOP-R

4.2.1.3. It is recommended that patients with a negative interim PET/CT after three cycles should receive one more cycle of CHOP-R

4.2.1.4. However, patients with a positive interim PET/CT should receive ISRT of 30–35 Gy

4.2.1.5. Another option is six cycles of CHOP-R if radiotherapy is to be avoided or not available.

4.2.2. Advance Stages III and IV or bulky stage

4.2.2.1. Six cycles of CHOP-R is the preferred treatment

4.2.2.2. PET/CT scan is highly recommended after completion of the six cycles of CHOP-R

4.2.2.3. In patients with positive PET/CT findings, ISRT may be an option in selected cases where biopsy is not possible and desirable

4.2.2.4. Confirmatory biopsy for positive PET cases is recommended prior to initiating the second line and subsequent therapies.

4.3. Dose modifications (CHOP-R)

4.3.1. In elderly patients aged >70 years, a 25% dose reduction of doxorubicin and cyclophosphamide in the first cycle is recommended. However, subsequent cycles should be given at maximum tolerable dose, with the aim of escalating to 100% of the dose (EL-3)[18]

4.3.2. When doxorubicin cannot be used due to risk of cardiac toxicity, it can be replaced with etoposide (R-CEOP) 50 mg/m^2 IV on Day 1, and 100 mg orally on Days 2 and 3

4.4. For discordant and transformed lymphoma, treatment must be directed at the most aggressive lymphoma.

4.5. For limited-stage composite indolent and aggressive lymphoma, treatment should be with CHOP-R plus IFRT.

4.6. Central nervous system prophylaxis

4.6.1 The risk of CNS relapse in aggressive lymphoma ranges from 1.6% to 5%. However, this risk can be higher (up to 50%) in patients with initial extranodal presentations (such as primary testicular lymphoma and paranasal sinus, orbital, epidural space, breast, kidney and adrenal involvement) or with poor prognostic features.[19,20] Most of the studies were carried out before rituximab was introduced, and it is considered that rituximab use may have resulted in lower CNS relapse rates. Currently, there is no consensus on the best CNS prophylaxis (EL-3)[21,22]

4.6.2 However, some studies recommended 2–4 cycles of high-dose intravenous methotrexate 3.5 g/m^2 given anytime between Days 10 and 14 of CHOP-R (EL-3).[23,24]

4.7. Management of relapsed DLBCL

4.7.1. Restaging should be done, including carrying out the blood work, CT of neck and CAP or PET/CT and bone marrow biopsy

4.7.2. For all patients aged <60 years, salvage chemotherapy with R-ESHAP (rituximab plus etoposide, methylprednisolone, high-dose cytarabine and cisplain) or R-GDP (rituximab plus gemcitabine, dexamethasone, cisplatin) for a maximum of three cycles followed by high-dose chemotherapy and autologous stem cell transplant should be considered (EL-1)[25,26]

4.7.3. Patients who are not transplant candidates could be treated with conventional chemotherapy such as ESHAP or GDP and with radiotherapy for symptomatic sites.[27]

4.8. Management of DLBCL patients with *MYC* rearrangement

4.8.1. Patients of this subgroup usually have an aggressive clinical course, and CHOP-R alone would give a poor outcome, especially in cases when *MYC* rearrangement is combined with mutated *BCL-2* or *BCL-6* (double hit) or mutated *BCL-2* and *BCL-6* (triple hit) (EL-3)[28,29]

4.8.2. For double hit (translocated *MYC* and translocated *BCL-2*), R-EPOCH for 6 cycles plus CNS prophylaxis is recommended (EL-3).[30,31]

5. FOLLOW-UP

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

5.2. History and physical examination should be noted in every visit
5.3. CBC with differential count and LDH evaluations should be made in every visit
5.4. Thyroid-stimulating hormone (TSH) test should be carried out at least once annually if the patient had received radiotherapy to the neck
5.5. CT of neck and CAP is required after completion of therapy, and if the findings are normal, no further routine imaging is required
5.6. Mammogram or breast MRI is required for women who received chest radiotherapy, beginning 10 years after diagnosis of lymphoma or when aged ≥40 years, whichever comes first
5.7. Annual influenza immunization is recommended.

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Conflicts of interest
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