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

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INTRODUCTION

Mantle cell lymphoma (MCL) is a type of B-cell lymphoma that falls in between the indolent and aggressive subtypes of non-Hodgkin's lymphoma (NHL). MCL combines the incurable feature of indolent lymphomas with the clinical course of aggressive lymphomas. According to the Saudi Cancer Registry, in 2015, NHL was the second and fifth most common cancer among Saudi male and female population, respectively, accounting for 6.9% of all cancers.[1] However, the incidence of MCL in Saudi Arabia is yet unknown, whereas in the United States and Europe, MCL constitutes about 7% of adult NHLs.[2,3]

In MCL, extranodal involvement is common, including bone marrow and peripheral blood. It also has a peculiar tendency to involve the gastrointestinal (GI) tract. Subclinical GI epithelial invasion without overt colonic polyposis is very common. Therefore, a high index of suspicion is required for detecting GI involvement in MCL patients, especially among those presenting with iron deficiency anemia.[4]

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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

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- 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.[5]

1. **PATHOLOGIC DIAGNOSIS**
   - 1.1.1. Excisional lymph node biopsy should be done to diagnose MCL (EL-3)
   - 1.1.2. If excisional lymph node biopsy is not feasible, then an incisional or core needle biopsy should be done (EL-3)
   - 1.1.3. Pathologically, the majority of MCLs consist of small lymphocytes with notched nuclei, and the architectural pattern of the lymph node is usually diffuse but may show a vaguely nodular or mantle zone growth pattern. A number of other morphologic variants have been recognized. The blastoid variant of MCL has a high mitotic rate and is clinically very aggressive. It can also mimic diffuse large B-cell lymphoma (EL-3)[6]
   - 1.1.4. Cyclin D1 expression is a hallmark of MCL. In cyclin D1-negative cases, SOX11 can be useful in the diagnosis (EL-3)[7]
   - 1.1.5. In terms of immunophenotype, MCL cells are typically positive for CD5, FMC7, bright CD20 and CD43, but negative for CD10 and CD23 (EL-3)[8]
   - 1.1.6. In terms of genetic variance, although not specific for MCL and found in other indolent NHLs, almost all MCL cases harbor the cyclin D1 translocation *t*(11;14) (q13;q32), which can be detected by fluorescence *in situ* hybridization or the traditional karyotypic analysis (EL-3).[9]

2. **DIAGNOSIS AND WORKUP**
   - 2.1. Evaluations should include complete history (i.e., age; gender; comorbidities; B-symptoms; Eastern Cooperative Oncology Group 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, central nervous system, GI tract, lung, bone and skin) (EL-3)
   - 2.2. **Investigations**
     - 2.2.1. Basic laboratory evaluations of all patients should include complete blood count (CBC) with differential, liver function test as well as routine blood chemistry including lactate dehydrogenase (LDH), electrolytes and calcium (EL-3).
     - 2.2.2. **Viral serology**
       - i. Hepatitis serology (hepatitis B surface antigen, core antibody and surface antibody as well as hepatitis C virus), and PCR for hepatitis B surface antigen-or core antibody-positive cases (EL-3)
       - ii. Testing for HIV is required (EL-3).
     - 2.2.3. **Imaging**
       - i. Computed tomography (CT) scan of neck and chest, abdomen and pelvis (CAP) should be performed in all cases (EL-3)
       - ii. Whole body positron emission tomography scan should be considered, especially in limited stage disease, prior to curative radiotherapy (EL-3).
     - 2.2.4. **Other tests**
       - i. Bone marrow biopsy is recommended as part of staging MCL patients (EL-3)
       - ii. Upper and lower GI scopes should be considered for patients with GI-related symptoms (EL-3)
       - iii. Pregnancy test must be done for women of childbearing age (EL-3).
   - 2.3. **Prognosis**
     - 2.3.1. Mantle Cell Lymphoma International Prognostic Index
       - 2.3.1.1. For MCL patients, the International Prognostic Index (IPI) is not adequate, as this score is not specific
       - 2.3.1.2. The use of a more specific score such as the Mantle Cell Lymphoma International Prognostic Index (MIPI) is recommended. MIPI uses age, performance status, LDH and WBC counts to separate patients into three risk groups (EL-1).[10]
     - 2.3.2. **Ki-67:** The use of immunohistochemistry stain for Ki-67 can provide an important prognostic value, as it classifies MCL patients into three groups. Patients with Ki-67 <10% have the best outcome (low risk) compared to patients with Ki-67 10%–29% (intermediate risk) and Ki-67 ≥30% (high risk) (EL-1).[11]

3. **TREATMENT**
   - 3.1. **Introduction to management:**
     - i. Treatment of MCL is based on the stage, age and comorbidities
     - ii. Limited stage is defined as Stage I or II, with no B-symptoms or bulky disease

iii. Advanced stage is defined as Stage III or IV, presence of B-symptoms or bulky disease regardless of the stage.

3.2. **Management of patients with limited stage disease:**

3.2.1. Localized disease is extremely rare in MCL

3.2.2. Involved site radiotherapy (ISRT) of 30 Gy or combination of a short treatment with immunochemotherapy (e.g., 3–4 cycles of rituximab plus cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP) or R-CHOP-like therapy) followed by ISRT is recommended (EL-3).[12]

3.3. **Management of patients with advanced stage disease:**

3.3.1. Given that advanced stage disease is relatively uncommon in MCL, there is no "standard" therapy or approach

3.3.2. Most patients have symptomatic disease and require treatment. However, few patients have a course similar to that of indolent lymphomas, and in these cases, a period of observation is recommended (EL-3)[13]

3.3.3. In MCL patients aged ≤60 years, dose-intensified therapies (e.g. autologous stem cell transplant-based regimens) should be considered.[14-16]

3.3.6. **Induction therapy**

3.3.6.1. **Aggressive regimens**:

3.3.6.1.1 The preferred regimen for advanced stages is alternating RCHOP/RDHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin) followed by myeloablative autologous stem cell transplant in patients achieving at least a partial response (≥75%)[17,18]

3.3.6.1.2. Another option is cyclophosphamide, vincristine, doxorubicin and dexamethasone (HyperCVAD) alternated with high-dose methotrexate and cytarabine plus rituximab (EL-2)[19,20]

3.3.6.1.3. For maintenance after autologous stem cell transplant, rituximab should be given every 8 weeks for 3 years (EL-1).[21]

3.3.6.2. **Less aggressive therapies for elderly or unfit patients:**

3.3.6.2.1. Combination of bendamustine and rituximab (EL-1)[22,23]

3.3.6.2.1. RCHOP followed by maintenance rituximab every 8 weeks until progression or intolerance (EL-1)[24]

3.3.6.2.1. Bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) (EL-1)[25]

3.3.6.2.1. Combination of lenalidomide and rituximab (EL-2).[26]

3.3.6.3. **Therapy for relapsed/refractory disease (second-line therapy):**

3.3.6.3.1. Ibrutinib in combination or without rituximab (EL-1)[27-30]

3.3.6.3.2. Combination of lenalidomide and rituximab (EL-2)[30,31]

3.3.6.3.3. Other preferred regimens are Venetoclax[32] and Acalabrutinib (EL-2).[33]

3.3.6.4. **Consolidation after second-line therapy:**

3.3.6.4.1 Allogeneic hematopoietic stem cell transplantation should be considered after achieving complete response with second-line therapy, if the patient is eligible for transplant (EL-3)[34]

3.3.6.4.2. Autologous transplant could be considered in relapsed patients if not performed as part of the initial treatment (EL-3).[14]

4. FOLLOW UP

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

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

4.3. CBC with differential count and LDH evaluations should be requested in every visit

4.4. CT of neck and CAP is required 3 months after completion of all therapy, and if the findings are normal, no further routine imaging is required

4.5. Annual influenza immunization is recommended (EL-3).[35]

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Conflicts of interest

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