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Saudi Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up of Mantle Cell Lymphoma (MCL)

National Cancer Center

(NCC)

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Mantle Cell Lymphoma (MCL): Saudi Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up

Overview

MCL is a type of B-cell lymphoma that falls in between the indolent and aggressive subtypes of non-Hodgkin lymphoma (NHL). MCL combines the incurability feature of indolent lymphomas with the aggressive course of aggressive lymphomas. NHL is the fourth most common cancer in Saudi Arabia.[1] According to the cancer incidence report from 2014, NHL constituted about 6.4% of all cancer among Saudi nationals. The incidence of MCL in Saudi Arabia is unknown. In the United States and Europe, MCL constitute about 7% of adult NHL.[2,3]

Extranodal involvement is common, including bone marrow and peripheral blood. MCL has a peculiar tendency to involve the GI tract. Subclinical GI epithelial invasion without overt colonic polyposis is very common and a high index of suspicion of the GI tract is needed when seeing a patient with MCL specially if presenting with iron deficiency anemia.[4]

1. Diagnosis

1.1. Pathology:

1.1.1. Optimally an excisional lymph node biopsy should be done to diagnose cases with MCL.

1.1.2. If excisional lymph node biopsy is not feasible, then an incisional or core needle biopsy should be done.

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. MCL blastoid variant has a high mitotic rate and is clinically very aggressive and can mimic diffuse large B-cell lymphoma (DLBCL). [5]

1.1.4. Cyclin D1 expression is a hallmark of MCL, however, SOX11 can be useful in diagnosing MCL in cases that are cyclin D1 negative.

1.2. **Immunophenotype**

1.2.1 MCL cells typically express: CD5+, FMC7+, bright CD20+, and CD43+ but CD10− and CD23.[6]

1.3. **Genetic tests**

1.3.1. Although not specific for MCL and can be seen in other indolent NHL, almost all MCL cases harbor the cyclin D1 translocation t(11;14)(q13;q32) which can be detected by FISH technique or by the traditional karyotypic analysis.

2. **Staging Workup**

2.1. **History and Physical:**

2.1.1. Complete history (age, gender, comorbidities, B-symptoms, ECOG performance status, hepatitis or HIV risk factors, medications, allergy to contrast or drugs, social and family history) and physical examination (Lymph nodes, Waldeyer's ring, spleen, liver, CNS, GI tract, lung, bone, and skin).

2.2. **Investigations**

2.2.1. **Basic blood work:** All patient should have the complete blood count (CBC) with differential, liver function test (LFT), routine blood chemistry including LDH, electrolytes and calcium.

2.2.2. **Viral serology**

i. Hepatitis serology (HB surface antigen, HB core antibody, HB surface antibody, HCV), and PCR for HB surface antigen positive or HB core antibody positive cases.

ii. Testing for human immunodeficiency virus (HIV) is required.

2.2.3. **Imaging**

i. CT neck and CAP (chest, abdomen and pelvis) should be performed in all cases.

ii. Whole body PET scan should be considered specially in limited stage disease prior to consideration of curative radiotherapy.

2.2.4. **Other tests**

i. Bone marrow biopsy is recommended as part of the staging of MCL patients.

ii. Upper and lower GI scopes should be considered for patients with GI related symptoms.

iii. Pregnancy test must be done for woman at childbearing age.

3. Prognosis

3.1. **MIPI/MIPI-C**

3.1.1. The international prognostic index (IPI) is not adequate for MCL patients as this score was not designed specifically for MCL.

3.1.2. The use of a more specific score for MCL is recommended such as the MCL international prognostic index (MIPI). MIPI uses age, performance status, LDH and WBC counts to separate patients into three risk groups.

3.2. **Ki-67:** The use of immunohistochemistry stain for Ki-67 can provide an important prognostic value through separating cases with MCL into three groups. Patients with Ki-67 < 10% have the best outcomes, followed by patients with 10-29% (intermediate risk), and those with 30% or more (high risk).

4. Management of MCL:

4.1. Introduction to Management:

i. Treatment of MCL is based on the stage, age and comorbidities.

ii. Limited stage defined as stage I or II, No B-symptoms and non-bulky disease.

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

4.2. Management of Limited Stage (localized disease is extremely rare in MCL):

4.2.1. Involved site radiotherapy (ISRT)[7] OR abbreviated treatment with immunochemotherapy followed by ISRT: e.g. 3-4 cycles of R-CHOP (or R-CHOP like).

4.3. Management of Advanced Stage:

4.3.1. Given that it is relatively uncommon, there is no “standard” therapy or approach to MCL.

4.3.2. Most patients have symptomatic disease and require treatment but a small number of cases have a course similar to the indolent lymphomas and a period of observation with watchful waiting is reasonable.[8]

4.3.3. For the younger patient (<60 with MCL), intensive therapy should be considered.

4.3.4. Several different intensive strategies appear to produce comparable results.

4.3.6. **Induction Therapy**

4.3.6.1. **Aggressive Regimens**:

a. Preferred option: alternating RCHOP/RDHAP followed by myeloablative ASCT in patients who achieve at least a partial response (> or = 75%).

OR

b. HyperCVAD: (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab.

4.3.6.2. **Maintenance after ASCT:**

a. Maintenance rituximab every 8 weeks x 3 years.[9]

4.3.6.3. **Less aggressive Therapies (for elderly or unfit):**

a. BR: (bendamustine + Rituximab).

b. RCHOP followed by maintenance rituximab every 8 weeks until progression or intolerance.

c. VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)[10]

d. Lenalidomide and rituximab.

4.3.7. **Relapsed/refractory Disease (second line):**

i. Ibrutinib +/- Rituximab.

ii. Lenalidomide and rituximab.

iii. Venetoclax.

iv. Acalabrutinib.

4.3.8. **Consolidation after second line:**

i. Allogeneic hematopoietic stem cell transplant should be considered after achieving complete response post second line therapy if the patient is eligible for transplant.

ii. Autologous transplant could be considered in relapsed patients if it was not performed as part of the initial treatment.

5. **Follow up:**

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

5.2. History and physical examination every visit.

5.3. CBC, differential and LDH every visit.

5.4. CT neck /CAP after 3 months of completion of all therapy, if normal then no further routine imaging is required.

5.5. Annual influenza immunization.

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