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

Magdy Kandil[1,2], Hani Alhashmi[3], Musa Alzahrani[4], Ayman Alhejazi[5], Ibraheem Motabi[6], Reyad Dada[7,8], Mubarak Al-Mansour[9,10], Ahmed Sagheir[11]

[1]Oncology Department, Prince Sultan Military Medical City, [4]Department of Medicine, College of Medicine, King Saud University, [5]Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Central Region, [6]Department of Adult Hematology and BMT, Comprehensive Cancer Center, King Fahad Medical City, [8]College of Medicine, Al-Faisal University, Riyadh, [3]Adult Hematology and Stem Cell Transplantation Department, King Fahad Specialist Hospital, Dammam, [7]Department of Oncology, King Faisal Specialist Hospital and Research Centre, [9]College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, [10]Adult Medical Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, Jeddah, [11]Oncology Institute, John Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, [2]Clinical Oncology Department, Cairo University, Giza, Egypt

Address for correspondence:
Dr. Mubarak Al-Mansour, Adult Medical Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, PO Box 9515, Jeddah 21423, Kingdom of Saudi Arabia.
E-mail: drmubarak55@hotmail.com
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INTRODUCTION

According to the Saudi Cancer Registry, in 2014, a total of 27 cases of marginal zone lymphoma (MZL) were diagnosed in the Kingdom of Saudi Arabia. MZL represents 3.8% (27 of 697) of all diagnosed non-Hodgkin's lymphomas in 2014. There were 11 males and 16 females, with a male-to-female ratio of 0.68:1.[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:

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- 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]

Definitions

In this guideline, the clinical, diagnostic and therapeutic modalities of the following three World Health Organization-classified MZL subtypes are described:[3]

1. Extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma)

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2. The splenic MZL (SMZL) (with or without villous lymphocytes)
3. Nodal MZL (NMZL) (with or without monocytoid B cells).

1. DIAGNOSIS AND WORK-UP

1.1. Evaluations should include clinical and physical examinations.

1.2. Laboratory evaluations of all patients should comprise complete blood count liver and renal function tests as well as blood chemistry including lactate dehydrogenase and beta-2 microglobulin. In a patient with hemolytic anemia, Coombs test is recommended.

1.3. Computed tomography (CT) scan of head, neck, chest, abdomen and pelvis should be performed in all cases. CT is the preferred imaging modality, as the performance of positron emission tomography (PET) scan in diagnosis is controversial (EL-3).[4]

1.4. Endoscopy

1.4.1. Gastric MALT: Endoscopic biopsies should be obtained from multiple gastroduodenal areas such as stomach, duodenum, gastro-esophageal junction and any abnormal-appearing site and *H. pylori* infection status should be evaluated (EL-2) (EL-3).[5] In addition, endoscopic ultrasound can optionally be used for evaluating regional lymph nodes and gastric wall infiltration (EL-3).[6]

1.4.2. Large intestine MALT: Colonoscopy and biopsy should be performed.

1.4.3. Lung MALT: Bronchoscopy and biopsy plus bronchoalveolar lavage is recommended.

1.5. Small intestine (immunoproliferative small intestinal disease [IPSID]): The tumor biopsy may be assessed for *Campylobacter jejuni* infection by polymerase chain reaction (PCR), immunohistochemistry or *in situ* hybridization.[7]

1.6. Thyroid MZL: Thyroid function tests must be carried out.

1.7. Salivary glands MALT: Ear, nose, throat examination and ultrasound should be performed. Anti-SSA or anti-SSB serum antibodies should be investigated for the diagnosis of primary Sjögren's syndrome (pSS).[8]

1.8. Ocular adnexa MALT: Perform magnetic resonance imaging (MRI) or CT scan and ophthalmologic examination. The tumor biopsy and blood mononuclear cells may be assessed for *Chlamydia psittaci* by PCR.[9]

1.9. Breast MZL: Mammography and MRI can optionally be performed.

1.10. Skin MZL: The tumor biopsy may be assessed for *Borrelia burgdorferi* infection (in endemic areas) by PCR.[10]

1.11. Whole-blood flow cytometry must be carried out. The tumor cells usually express CD19, CD27, CD20 and CD79b, whereas CD5, CD10, CD23 and CD43 are usually negative. FMC7 expression should also be assessed, although it can be either positive or negative. In addition, the kappa/lambda expression must also be analyzed.[11,12]

1.12. Serology tests for hepatitis C, hepatitis B and human immunodeficiency viruses should be carried out.

1.13. Bone marrow aspirate and trephine biopsy are recommended.[13]

2. PATHOLOGIC DIAGNOSIS

2.1. Microscopy

2.1.1 Nodal MZL: B-cell neoplasm is composed of small-and medium-sized cells that involve the mantle and marginal zones of peripheral lymph nodes.

2.1.2 Extranodal MZL: Neoplasm is primarily composed of small B lymphocytes, frequently with moderately abundant pale cytoplasm (monocytoid cells) and a predilection for involvement of mucosal sites.

2.1.3 Splenic MZL: B-cell neoplasm is composed of small-and medium-sized cells that involve the mantle and marginal zones of splenic follicles and red pulp. It lacks features of NMLZ or MALT lymphoma, with no peripheral node or extranodal tissue involvements

2.1.4 MZLs should be differentiated from other small cell lymphomas such as small lymphocytic lymphoma/chronic lymphocytic leukemia, mantle cell lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma and hairy cell leukemia.[3]

2.1.5 The immunophenotypic features of MZL includes negative in CD5, CD10, CD23, CD43, nuclear cyclin D1 and CD103. CD20+ and CD79a+ are positive, but variable in sIGM.[14]

2.1.6 Fluorescence *in situ* hybridization (FISH)/PCR and cytogenetics (Optional):[15,16] t (11,18) (mandatory), t (1,14), t (3,14), t (11,14), t (14,18), del (7q) and del (13q).

2.1.6.1 Trisomy 3q, deletion or translocation of 7q32 and 13q14, trisomy 18, 17q isochromosome, structural abnormalities of chr

1 and absence of t (11;14) are observed in SMZL.

2.1.6.2 Gain of chromosomes 3, 18q23 and loss of 7q are characteristics of NMZL.

2.2.6.3 MYD88 status to differentiate Waldenström's macroglobulinemia vs MZL with plasmacytic differentiation.[17]

3. STAGING

3.1 The Lugano modification of Ann Arbor staging system should be used for staging MZL [Table 1].[13]

3.2 For gastric MZL, the Lugano staging system for gastrointestinal lymphomas, or its equivalent, should be used [Table 2].[18]

3.3 Prognostic factors

3.1 SMZL prognostic score includes three variables: Hemoglobin level of <12 g/dl, LDH higher than normal levels and albumin level of <3.5 g/dl. Using these variables, patients can be segregated into low-, intermediate-and high-risk groups.[19] Progression can be associated with histological transformation to diffuse large B-cell lymphoma, and it is more common in cases where the peripheral lymph node is involved.[20,21]

4. MANAGEMENT

4.1 Localized MZL

4.1.1 Localized NMZL, Stage I or Contiguous stage II (non-gastric or non-SMZL): The preferred treatment is involved site radiotherapy (ISRT)/involved field radiotherapy (IFRT) of 30 Gy in 15 fractions over 3 weeks (EL-1).[22-25]

4.1.2 Localized gastric MZL stage I and II:

For all patients with gastric MALT lymphomas, irrespective of the stage or histological grade, *H. pylori* eradication therapy should be prescribed (EL-3).[26-28] For evaluating the outcome, urea breath or monoclonal stool antigen tests can be used 6–8 weeks after the therapy had been initiated and at least 2 weeks after the proton pump inhibitor (PPI) has been withdrawn.[29-31] Currently, there are three recommended regimens. In Regimen #1, omeprazole 20 mg (PO), amoxicillin 1 g (PO)

Table 1: Lugano Modification of Ann Arbor Staging System

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contagious extranodal involvement
II Bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous Extralymphatic involvement	Not applicable

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors. The extent of disease is determined by PET-CT for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring and spleen are considered nodal tissue. PET – Positron emission tomography; CT – Computed tomography

Table 2: Staging system gastric marginal zone lymphoma

Lugano staging system for gastrointestinal lymphoma	Lugano Modification of Ann Arbor staging system	TNM staging system adapted for gastric lymphoma	Tumor extension
Stage I_E Confined to GI tract (single primary noncontiguous)			
I_{E1}=Mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
I_{E2}=Muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
	I_E	T3 N0 M0	Serosa
Stage II_E Extending into the abdomen			
II_{E1}=Local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
II_{E2}=Distant nodal involvement	II_E	T1-3 N2 M0	More distant regional nodes
Stage II_E Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement	IV	T1-4 N3 M0 T1-4 N1-3 M1	Lymph nodes on I sides of the diaphragm distant metastases, bone marrow and/or extranodal sites)

and clarithromycin 500 mg (PO) are prescribed twice daily. This is the preferred treatment regimen. In Regimen #2, omeprazole 20 mg (PO), metronidazole 500 mg (PO) and clarithromycin 500 mg (PO) are prescribed twice daily. This regimen is for patients allergic to penicillin. In Regimen #3, omeprazole 20 mg is prescribed twice daily (PO) and tetracycline 500 mg (PO), metronidazole 500 mg (PO) and bismuth 525 mg (PO) are prescribed four times a day (EL-3). For all three regimens, the treatment duration is 10–14 days. Other proton pump inhibitors may be substituted at equivalent dosages (EL-2).[32]

If the outcome test is positive for *H. pylori* after 2 months of using Regimen 1, it is recommended to use Regimen 2 and repeat esophago-gastro-duodenoscopy (EGD) at 3 and 6 months. In patients negative for *H. pylori* but positive for lymphoma, repeat EGD every 6 months for 2 years, and yearly thereafter. In asymptomatic patients negative for *H. pylori* but positive for lymphoma, repeat EGD every 3–6 months. Tests to confirm eradication should be performed at least four weeks after completion of antibiotic treatment.[33] PPIs should be withdrawn 1-2 weeks prior to conducting the test for reducing chances of false-negative results. Serologic testing should not be performed to confirm eradication, as patients may continue to have antibodies even after eradication (EL-2).[34]

To assess response to treatment, Groupe d' Etude des Lymphomes de l' Adulte (GELA) histological scoring system is recommended for comparing with previous biopsies [Table 3] (EL-2).[35]

If symptomatic, deep invasion, lymph nodes or positive for lymphoma after 12–18 months or positive FISH for t (11:18), the patients should receive ISRT of 30 Gy in 20 fractions over 4 weeks.[22,23]

4.1.3 Localized non-gastric MALT lymphoma Stages I and II:

The treatment of choice is ISRT of 24–30 Gy in 12–20 fractions over 3–4 weeks (EL-1).[22-24] Patients with small intestine, colon, breast, thyroid or lung MALTs are treated by surgery (EL-3).[36] IPSID patients positive for *C. jejuni* are treated with ciprofloxacin, azithromycin or levofloxacin for 5 days post-surgery (EL-3).[37] Ocular adnexa patients positive for *C. psittaci* in endemic areas are treated with doxycycline 100 mg twice daily for 14 days (EL-2).[38] However, in refractory or *C. psittaci* negative ocular adnexal MZL patients, ISRT should be used. Skin MZL can be treated with surgery or ISRT, depending on size and cosmesis (EL-2).[24]

4.1.4 Localized SMZL: Indications for treatment include progressive or painful splenomegaly and one of the following symptomatic/progressive cytopenias: hemoglobin <10 g/dl, platelets <80,000/μl or neutrophils <1000/μl. It should be noted that autoimmune hemolytic anemia should be specifically treated.

4.1.4.1 In asymptomatic patients with no cytopenia or splenomegaly, only observation is adequate (EL-2).[39,40]

4.1.4.2 Refer patients with splenomegaly and hepatitis C to an hepatologist for treating hepatitis C (EL-2),[41,42] and if the patient is not responding, treat as hepatitis C virus genotypes 1, 3, 4 and 6.

4.1.4.3 In patients with splenomegaly but no hepatitis C, symptomatic cytopenia can be treated with splenectomy[42,43] or rituximab (EL-2).[44-46]

4.1.5 For frail patients in whom radiotherapy or surgery is not suitable, rituximab can be used (EL-2).[47] For patients allergic to rituximab, it is recommended to use single-agent chemotherapy such as chlorambucil (EL-1),[48,49] bendamustine (EL-2)[50] or cyclophosphamide[51] (EL-3) along with cladribine (EL-3).[52]

4.2 Stage II non-contiguous, III and IV:

4.2.1 In asymptomatic patients, only observation is adequate (EL-2).[53]

Table 3: Groupe d' Etude des Lymphomes de l' Adulte histological grading system for posttreatment evaluation of gastric mucosa-associated lymphoid tissue lymphoma

Score	Lymphoid infiltrate	LEL	Stromal changes
CR	Absent or scattered plasma cells and small lymphoid cells in the LP	Absent	Normal or empty LP and/or fibrosis
pMRD	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD	Dense, diffuse, or nodular extending around glands in the LP	Focal LEL or absent	Focal empty LP and/or fibrosis
NC	Dense, diffuse, or nodular	Present, "may be absent"	NCs

CR – Complete histological remission; pMRD – Probable minimal residual disease; rRD – Responding residual disease; NCs – No changes; LP – Lamina propria; MM – Muscularis mucosa; SM – Submucosa; LELs – Lymphoepithelial lesions

4.2.2 In frail patients or those with minimal symptoms, single-agent rituximab[47,53] (weekly x4 doses) (EL-1) or chlorambucil–rituximab should be used (EL-1).[47]

Maintenance rituximab is optional and can be administered every 2 months × 4 doses[54] or every 3 months until progression (EL-2).[36,55]

For patients allergic to rituximab, it is recommended to use single-agent chemotherapy such as chlorambucil (EL-1),[47-49] bendamustine (EL-2)[50] or cyclophosphamide (EL-3)[51] along with cladribine (EL-3).[52]

4.2.3 In symptomatic patients, chemo-immunotherapy is indicated. Cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab (CHOP-R); cyclophosphamide, vincristine and prednisone plus rituximab (CVP-R); or bendamustine–rituximab can be used (EL-1).[56,57]

4.2.4 Palliative ISRT is recommended for symptomatic disease (4 Gy in 2 fractions or 30 Gy in 15 fractions) and bulky disease >7 cm (30 Gy in 15 fractions) (EL-3).[22-24]

4.2.5 In patients with refractory disease, bendamustine–obinutuzumab therapy with maintenance obinutuzumab every 8 weeks for 12 doses is an effective treatment option (EL-1).[58,59] Other options include ibrutinib (EL-2),[60] lenalidomide–rituximab (EL-2),[61] idelalisib (EL-2),[62] cladribine–rituximab (EL-2)[63] and fludarabine–rituximab (EL-2).[64]

5. ASSESSMENT OF RESPONSE

5.1 Splenic MZL: The assess the response to treatment, the criteria of Centro Nacional de Investigaciones Oncologicas, Madrid, Spain, is recommended (EL-2).[65]

5.1.1 Complete response is defined as:

i. Resolution of organomegaly (i.e., the longitudinal diameter of spleen is <13 cm).
ii. Hemoglobin levels of >12 g/dl, platelets >100 × 109/L and neutrophils >1.5 × 109/L.
iii. No evidence of circulating clonal B cells by flow cytometry (light chain restricted B cells).
iv. No evidence of bone marrow infiltration detected by immunohistochemistry.
v. Optional: A negative DaT (Dopamine transporter) and normal PET scan (if positive at diagnosis).

5.1.2 Partial response is defined as:

i. Regression of ≥50% in all the measurable disease manifestations.
ii. No new sites of disease.
iii. Improvement in cytopenias.
iv. Decrease in infiltration and improvement of hemopoietic reserve at bone marrow biopsy.

5.1.3 No response is when there is <10% improvement of the disease manifestations.

5.1.4 Progression is defined as an increase of >50% in the measurable signs of the disease from baseline.

5.1.5 Relapse is defined as reappearance of any measurable signs of the disease.

5.2 Gastric MZL: The GELA scoring system is recommended for comparing with previous biopsies to assess response to treatment [Table 2] (EL-2).[35]

5.3 Nodal MZL and other extranodal non-gastric and non-SMZL: The Lugano criteria for response assessment using CT or PET-CT based response is recommended (EL-3).[13]

6. FOLLOW-UP

There are no standards for follow up (EL-3).[12,36] For patients who are asymptomatic after treatment, physical examination, blood counts and biochemistry is recommended every 3 months for the first 2 years, then every 6 months for 5 years, and then annually for at least 5 years.[45] The follow-up intervals should be shortened if there is an increase in splenomegaly and/or occurrence of cytopenia(s). A CT scan or bone marrow biopsy is not indicated unless signs of disease progression are noted. For gastric MZL, the endoscopy interval after achieving complete remission is not yet established. Nonetheless, we recommend endoscopy once every 3 months until complete remission is achieved, following which every 6–12 months for 2 years and then annually for 3 years to exclude secondary gastric adenocarcinoma (EL-3).[66]

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Conflicts of interest

There are no conflicts of interest.

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