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POSITION PAPER

Marginal zone lymphomas: a consensus practice statement from the Australasian Lymphoma Alliance

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Abstract

Marginal zone lymphomas (MZLs) are a rare, indolent group of non-Hodgkin lymphomas with different diagnostic, genetic and clinical features and therapeutic implications. The most common is extranodal MZL of mucosa-associated lymphoid tissue, followed by splenic MZL and nodal MZL. Patients with MZL generally have good outcomes with long survival rates but frequently have a relapsing/remitting course requiring several lines of therapy. The heterogeneous presentation and relapsing course present the clinician with several diagnostic and therapeutic challenges. This position statement presents evidence-based recommendations in the setting of Australia and New Zealand.

Introduction

Marginal zone lymphoma (MZL) is a heterogeneous group of indolent lymphomas, collectively comprising approximately 5–15% of non-Hodgkin lymphoma (NHL).[1,2] The incidence in Australia and New Zealand is not readily defined, but it is estimated to be 490 new cases *per annum*.[3] The three main subtypes include extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT; 50–70%), splenic (20%) and nodal (10%).[1,2,4,5]

This practice statement provides healthcare professionals with general guidance on the diagnosis, treatment and follow-up of patients with MZL in the Australian and New Zealand setting.

Methodology

This consensus practice statement was developed by a panel of lymphoma experts with particular interest in MZL in accordance with the Australasian Lymphoma Alliance consensus practice statement development policy (Supporting Information).

Diagnosis, workup and staging

The diagnostic and staging pathway is dependent on the subtype of MZL and site involved. Diagnosis should fulfil the World Health Organization (WHO) 2022 classification criteria and requires an adequate biopsy to

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distinguish MZL from other mature B-cell lymphomas (Table 1). In certain situations, such as splenic MZL (SMZL), biopsy may not be feasible and the diagnosis is based on imaging in conjunction with evidence of MZL in the peripheral blood. Characteristics listed are 'classical presentations' and are not necessarily present in every case.[2]

Details of histopathological features of the different subtypes of MZL are detailed in Table 2 and Supporting Information.[2,6]

Extranodal MZL

EMZL of MALT is classically driven by chronic inflammation from infectious pathogens or autoimmunity, and can arise in most epithelial tissues.[9] EMZL generally remains localised to the tissue of origin, though recurrent/multifocal tissue involvement and disseminated disease may occur.[10] Clinical presentation is dependent on the site of involvement, with typical symptoms including dyspepsia and occult bleeding in gastric EMZL; periorbital masses, red eyes and visual field defects in ocular EMZL; recurrent respiratory infections and incidental radiological lung nodules in pulmonary EMZL; and skin nodules and papules in cutaneous EMZL.

Staging investigations are dependent on the original site of involvement, as outlined in Table 2. Fewer than 10% of patients with clinically and radiologically localised MALT have occult bone marrow involvement, and bone marrow biopsy may reasonably be limited to patients with cytopenias or other concerning features. Positron emission tomography (PET) has limited utility in gastric and ocular EMZL due to poor 18F-FDG uptake, though it may be of use in select patients with EMZL occurring at other sites, and where the differential diagnosis includes nodal MZL with involvement of an extranodal site.[11]

Gastric extranodal MZL

Gastric EMZL accounts for 40% of all gastric lymphoma cases.[12–14] A systematic review of gastric MALT lymphoma found an association with *Helicobacter pylori* infection in 88% of 2000 cases.[15] Translocation (t)(11;18)(q21;q21) BIRC3-MALT1 is present in 15–40% of gastric

Table 1 Differential diagnoses

Differential diagnosis	Characteristics
Mantle cell lymphoma	Small- to medium-sized cells with slightly irregular nuclear contours, inconspicuous nucleoli and scant cytoplasm Immunophenotype CD5+, CD23−, CD200−, overexpression of Cyclin D1. In rare cyclin-D1 negative cases, SOX11 expression can be diagnostic Presence of t(11;14) translocation
Follicular lymphoma	Mixture of centroblasts and centrocytes. Centrocytes are slightly larger than small lymphocytes, with angulated or cleaved nuclei. Centroblasts are large cells with visible cytoplasm and round or oval nuclei with vesicular chromatin and multiple nucleoli Immunophenotype CD10+ Presence of t(14;18) translocation
Waldenstrom macroglobulinaemia (WM)	Small lymphocytes, plasmacytoid cells and plasma cells Immunophenotype CD5− and CD10−. CD25 expression is more commonly expressed in WM, while CD22 expression is more suggestive of SMZL. IgM paraprotein is invariably present in WM but can sometimes be detected in MZL. MYD88 L365P mutation is present in >90% and CXCR4 mutation in 30% of WM. MYD88 mutation is found in up to 15% of MZL.[7,8]
Small lymphocytic lymphoma	Small lymphocytes Immunophenotype CD5+, CD23+ and CD200+ Trisomy 12, deletion of chromosome 11q23, 13q14 and 17p
Splenic diffuse red pulp small cell lymphoma	Diffuse splenic infiltration and mixed BM pattern of infiltration, monomorphous cytology or morphology. Cyclin D3+, CD11c+, CD180+ and CD200 dim. Del 7q, CCND3 and BCOR present in 25% of patients.
Splenic B-cell lymphoma with prominent nucleoli (formerly known as hairy cell leukaemia variant)	Diffuse splenic infiltration, monomorphous cells, intermediate between prolymphocytes and hairy cells. Immunophenotype CD11c+ and CD103+. Del(7q) present in 20% of patients.
Hairy cell leukaemia (HCL)	Diffuse splenic infiltration, monomorphous hairy cells. Immunophenotype CD11c+, CD180+, CD200+, CD103+ and CD123+. BRAF pV600E present in >95% of HCL.

MZL, marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.

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Table 2 Staging investigations and workup

MZL subtype	Test	Comments
All subtypes		
	History and examination: • B symptoms • Performance status • Underlying autoimmune conditions • Physical examination including assessment for lymphadenopathy, splenomegaly, organomegaly and extranodal sites (e.g. ocular adnexa, cutaneous, breast and thyroid)	All patients
	Diagnostic biopsy • Immunophenotyping for CD20, CD5, CD23, CD10, cyclin D1 and SOX11, follicular dendritic markers (CD21, CD35) • Cytogenetic studies, including t(11;18), t(11;14), t(1;14), t(3;14), t(14;18), CLL FISH panel • Molecular studies: ○ MYD88 L265P • IHC, PCR, serology or FISH for underlying cause	An extended panel may be required to distinguish MZL from other small B-cell lymphomas Not required in all patients but can be useful in some to exclude differential diagnoses t(11;18) may predict response to *H. pylori* eradication in gastric MZL. Testing is not readily available Although MYD88 gene mutations can be found in up to 15%[7,8] of MZL, it is expressed in >90% of patients with lymphoplasmacytic lymphoma and can hence be useful in the diagnosis *Helicobacter pylori* status should be evaluated in all gastric EMZL. Assessment for *Campylobacter jejuni* in intestinal EMZL and *Chlamydia psittaci* in ocular EMZL may also be considered
	Blood tests: • Full blood cell count and blood film • Biochemistry (including electrolytes, creatinine, urea and liver function tests) • Immunoglobulins • Protein electrophoresis • LDH • Serology for HCV, • HBV and HIV • Cryoglobulins (if HCV positive)	All patients HCV has been linked with EMZL, SMZL and NMZL[38,39] HBV serology should be performed prior to anti-CD20 therapy due to the risk of viral reactivation HIV serology may be deferred until prior to lymphoma therapy
	Imaging: • CT neck, chest, abdomen and pelvis with contrast • PET scan	All patients If suspecting large cell transformation or to confirm stage I/II disease prior to treatment
	Pre-treatment assessments: • Cardiac assessment (MUGA or echocardiogram) • Pregnancy test	If anthracycline chemotherapy is considered
SMZL		
	Immunophenotyping of peripheral blood BMAT	
	Assessment for autoimmune phenomena: • Direct antiglobulin test, haptoglobin, reticulocyte count, cold agglutinin screen • Coagulation studies, von Willebrand factor studies • Antiphospholipid antibodies • C4, C1 inhibitor antigenic level and function	Investigations should be directed by clinical presentation
NMZL		
	BMAT	May be useful to confirm stage I/II disease prior to therapy
EMZL Investigations should be guided by clinical presentation		
	BMAT	May be useful to confirm localised disease prior to therapy

Table 2 *Continued*

MZL subtype	Test	Comments
Gastric	• Endoscopy with biopsies taken of abnormal sites plus random biopsies of stomach, duodenum and gastroesophageal junction • Serology, faecal antigen and/or urea breath test for *H. pylori* • Endoscopic ultrasound	Assessment for *H. pylori* should include immunohistochemistry If the gastric biopsy is negative for *H. pylori*, the findings should be confirmed with alternative testing such as serology or breath test or stool antigen. Useful to assess gastric wall infiltration and local nodal involvement in gastric MALT[6,19]
Intestinal	Endoscopy and/or colonoscopy	
Ocular	CT and/or MRI orbits	
Salivary glands	Clinical history of dry eyes/dry mouth Anti-Ro/SSA and anti-La/SSB antibodies, ANA and rheumatoid factor	To assess for underlying Sjogren syndrome
Thyroid	Thyroid ultrasound Thyroid function tests	To assess for underlying Hashimoto thyroiditis
Breast	Breast imaging (mammography, ultrasound and/or MRI)	
Lung	Bronchoscopy and bronchoalveolar lavage *Campylobacter jejuni*, *Borrelia burgdorferi*, *Chlamydia* testing	To obtain diagnostic specimen Serology is frequently negative, molecular testing can be considered but is not widely available

ANA, Anti-Ro/SSA and anti-La/SSB antibodies; BMAT, Bone Marrow Aspriate and Trephine; CT, computed tomography; EMZL, extranodal marginal zone lymphoma; MRI, magnetic resonance imaging; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.

EMZL cases.[16] This translocation or amplification of the MALT1 locus has been associated with a worse prognosis.[13,17]

Conventionally, gastric EMZL is staged according to the Lugano staging system for gastrointestinal lymphoma,[18] although staging systems incorporating modified TMN criteria, including the depth of gastric wall extension, have been proposed (Table 3).[19] Small lesions are often not detectable by PET or computed tomography (CT), necessitating endoscopic examination.

Nongastric extranodal MZL

Infectious agents implicated in the aetiology of EMZL include: *Borrelia burgdorferi* (cutaneous EMZL), *Campylobacter jejuni* (small bowel EMZL[20]) and *Chlamydia psittaci* (CP; ocular EMZL[21]). *Achromobacter xylosoxidans* may be associated with pulmonary MZL but aetiology remains unproven. Although there is a reported link between CP and ocular EMZL,[21,22] it is rare in Australia and testing is not standardised. Autoimmune chronic inflammation in the salivary gland (Sjogren syndrome) and thyroid gland (Hashimoto thyroiditis) often precedes the development of EMZL in these areas.[23] Primary cutaneous B-cell lymphomas are outside of the scope of this paper.

Splenic MZL

The fifth WHO classification of tumours of haemopoietic and lymphoid tissues outlines several splenic lymphoma entities that can be challenging to differentiate.[24] Typical sites of disease in SMZL include the spleen, splenic hilar lymph nodes, bone marrow and often the peripheral blood.[25] Patients frequently present with incidental lymphocytosis, and in advanced-stage disease, may present with splenomegaly and/or cytopenias due to marrow infiltration, hypersplenism or immune-mediated destruction.[26,27] Nodal involvement (apart from localised splenic hilar nodes) and systemic B symptoms are uncommon and should prompt investigation to exclude large cell transformation, which occurs in 5–10% of cases.[28] Autoimmune disorders are present in 20% of patients and include immune thrombocytopenia, haemolytic anaemia/cold agglutinin disease, acquired von Willebrand disease, antiphospholipid syndrome and acquired C1 esterase inhibitor deficiency.[27,29,30] An association between hepatitis C virus (HCV) infection and SMZL is well established.[28]

In most cases, peripheral blood morphology and immunophenotype as well as bone marrow histology are adequate to distinguish SMZL from other B-cell lymphomas with splenic involvement.[10,31] Typical immunophenotype and differential diagnoses are outlined in Table 1.

Table 3 Management of gastric EMZL[10,62]

Lugano stage	Distribution	First-line therapy (Hp+)	First-line therapy (Hp− or t(11;18))
I	I(1): mucosa or submucosa I(2): muscularis propria	Antibiotics	Consider trial of antibiotics Local radiotherapy†
II(1)	II(1): perigastric nodes	Antibiotics	Consider trial of antibiotics Local radiotherapy†
II(2)	II(2): distant abdominal nodes	Antibiotics R-Chemotherapy‡	Consider trial of antibiotics R-Chemotherapy‡
IIE	Penetration of serosa to involve adjacent organs or tissues	Antibiotics R-Chemotherapy‡	Consider trial of antibiotics R-Chemotherapy‡
IV	Nodes on both sides of diaphragm, bone marrow involvement, additional extranodal sites	Antibiotics R-Chemotherapy may be required	Consider trial of antibiotics R-Chemotherapy may be required

†Radiotherapy = 24–30 Gy to stomach and perigastric nodes.
‡If symptomatic disease.

Nodal MZL

Nodal MZL classically presents with painless lymphadenopathy and has an indolent clinical course.[32] Approximately half of patients present with stage III/IV and up to one-third with bulky disease (tumour >5 cm).[33] Systemic B symptoms and elevation in lactate dehydrogenase (LDH) may suggest large cell transformation, which occurs in 5–10% of patients.[34,35] NMZL has been associated with HCV and chronic inflammation, but unlike SMZL and EMZL, the association with autoimmunity is uncommon. An IgM paraproteinaemia is observed in approximately 10% of patients, which may create challenges in distinguishing NMZL from Waldenstrom macroglobulinaemia.[36] NMZL is similar to other MZLs in morphological and immunophenotypic features.

Paediatric MZL

Paediatric NMZL (PNMZL) is a rare indolent mature B-cell lymphoma, predominantly occurring in the head and neck region of male adolescents. Unlike adult NMZL, these lymphomas are characterised by localised disease and excellent prognosis without systemic treatment. A recent multicentre study showed overlapping morphological features between PNMZL and paediatric-type follicular lymphoma in twothirds of cases and shared genetic features that are distinct from adult NMZL.[37]

Prognostic factors

Although EMZL outcomes are heterogeneous, patients generally have a good prognosis with an overall survival (OS) of >80% at 10 years. The revised MALT Prognostic Index (MALT-IPI) score is a validated and updated risk score developed to identify patients with higher-risk diseases.[40] Histologic transformation is more likely in those with an elevated LDH, more than four nodal sites involved and failure to achieve a complete remission after initial treatment. Patients with histologic transformation have a lower 5-year OS (65% vs 86%).[41] SMZL is generally indolent, with median OS of >10 years.[42] Although survival rates have improved in the rituximab era, some patients have a more aggressive course with a median survival of 18 months.[43] Two main prognostic indices for SMZL are the Splenic Marginal Zone Lymphoma Study Group (SMZLSG) and the Intergruppo Italiano Linfomi (IIL) prognostic index.[44,45] Both scores distinguish high-risk groups, but the SMZLSG is better at distinguishing the low- and intermediate-risk groups. Other prognostic fars include TP53 deletion and/or mutation and expression of NF-KB signature genes, but these are not routinely available. The 10-year risk of transformation has been reported as 17% with a 5-year OS post-transformation of 42%.[46] In NMZL, increased age and advanced stage have been associated with an adverse prognosis.[47] There are no validated prognostic scoring systems in NMZL and data on the applicability of the Follicular Lymphoma International Prognostic Index are conflicting. Marginal Zone Lymphoma International Prognostic Index (MZL-IPI) is a recently validated prognostic score for all patients with MZL who are being considered for systemic therapy.[48]

Treatment

When considering therapy for MZL it is important to appreciate that most patients with MZL will have a normal life expectancy. Long-term toxicity is, therefore, an important consideration.

Extranodal MZL

Gastric MZL

H. pylori eradication with a proton pump inhibitor (PPI) and dual antibiotics is considered first-line therapy for all

gastric EMZL, taking into account local antibiotic resistance patterns.[49] In *H. pylori*-positive early-stage disease, *H. pylori* eradication therapy is reported to be associated with complete histologic remission in 75% of patients,[50] with a median time to complete response (CR) of 3 months.[51] If *H. pylori* eradication is not achieved, second-line antibiotic and PPI regimens should be attempted.

Patients with *H. pylori*-negative gastric EMZL may still be considered for antibiotic therapy with reported response rates of 25% in a small case series.[52] Although t(11;18) has been associated with poor response to antibiotics, it is not considered a contraindication to *H. pylori* eradication therapy. Note that random biopsies often show persistence of tumour on histopathology and/or molecular testing for >12 months after successful treatment; hence, treatment decisions should not be based on these findings. Persistence of B-cell monoclonality has been reported in 27–61% of patients with complete histological response to eradication therapy with follow-up of >60 months, and is a recognised risk factor for treatment failure.[53,54] For patients with early-stage *H. pylori*-positive gastric EMZL, the 5-year survival after *H. pylori* eradication therapy is 90%.[54]

For stage I/II gastric EMZL, radiation therapy (RT) to the stomach +/− involved perigastric lymph nodes is delivered with curative intent, and should be considered for patients with disease that is antibiotic-refractory or demonstrates minimal endoscopic response 3–6 months after antibiotic therapy.[55,56] Conventionally dosed RT (24–30 Gy in 1.5–2 Gy per fraction) achieves CR rates of 98–100%[55,57–59] with low risk of local relapse. Contouring guidelines for involved site RT (ISRT) are available from the International Lymphoma Radiation Oncology Group (ILROG).[60] Modern RT techniques, including deep-inspiration breath-hold and image-guided RT techniques, allow for reduced RT doses to nearby organs, including kidney and heart.[61] Overall, 5-year survival for patients with stage I/II gastric EMZL treated with gastric RT is 98%.[58]

Ocular-adnexal EMZL

In patients with ocular-adnexal EMZL and minimal symptoms, it may be reasonable to consider a first-line trial of antibiotics. Doxycycline 100 mg oral twice a day for 3 weeks is the most commonly used regimen. Published overall response rates (ORRs) vary (27–65%).[63–66] Higher response rates are seen in those with proven *C. psittaci* positivity, although responses have also been reported in *C. psittaci*-negative cases. Local progression/relapse without systemic spread is the most common pattern of treatment failure in doxycycline-treated patients (34%).[63,65] Given the *C. psittaci* status is highly associated with response, we recommend proceeding to RT if no tumour response is observed at 3 months.

ISRT is a highly effective, curative treatment option for patients with unilateral or bilateral ocular-adnexal EMZL, and is the conventional standard of care. The recommended RT dose has decreased to 24–25 Gy (in 1.5–2 Gy per fraction)[67,68] with multiple series showing preservation of disease control, with CR rates of 99–100% and high rates of durable local disease control, while reducing toxicity risks. Emerging evidence for ultra-low-dose RT (4 Gy in two fractions) suggests high ORRs (CR rate, 75–86%), with minimal risk of toxicities and greater patient convenience; however, long-term relapse data are lacking.[69,70] Guidelines from ILROG are available to guide contouring for uniformity in ISRT.[60]

Nongastric, nonocular adnexal EMZL

Nongastric and nonocular primary EMZL are rare. For patients with localised disease, curative-intent ISRT is associated with excellent disease control; 24–30 Gy (in 1.5–2 Gy per fraction) produces high rates of CR and local disease control, with OS of 95% at 5 years.[71] Contouring guidelines are available from ILROG for standardisation of ISRT for extranodal lymphomas.[60]

Other reported treatment modalities for EMZL include surgical excision, rituximab monotherapy and observation.[71,72] Patients with positive margins after surgery may also be considered for postoperative ISRT. Treatment of HCV may result in regression of HCV-related EMZL.[73]

Advanced-stage disease

Symptomatic disease should be treated. Several chemoimmunotherapy (CIT) regimens cit have been demonstrated to be effective. In the IELSG-19 (International Extranodal Lymphoma Study Group 19) trial,[74] 89 patients were treated with six cycles of rituximab-chlorambucil, achieving CR rates of 91% in gastric and 72% in nongastric disease. Five-year progression-free survival (PFS) was 72%. The MALT 2008-01 (GELTAMO (Grupo Español de Linfomas/Trasplante de Médula Ósea)) study reported the bendamustine and rituximab (BR) combination to be highly effective with an ORR of 100% and a CR of 98%. The majority (75%) of patients achieved CR after three cycles and therefore only received four cycles in total. The estimated 7-year PFS was 93%, which favourably compares with the IELSG-19 data. This regimen is well tolerated and in most patients can be completed in four cycles, which is significantly shorter than 6 months of R-chlorambucil. Importantly, the response to BR is independent of t(11;18) status. Low-

dose radiotherapy (4 Gy in two fractions) is an excellent palliative therapy for symptomatic disease.[75]

Recommendations

- First-line treatment for gastric EMZL is antibiotic-based eradication therapy (III, A).
- ISRT should be considered for patients with symptomatic stage I/II gastric EMZL who have had minimal endoscopic response 3–6 months after antibiotic therapy (III, A) or if urgent therapy is required for symptomatic disease and there is insufficient time to trial antibiotic therapy. It may also be considered in patients with gastric EMZL who are *H. pylori* negative and/or in the presence of t(11;18).
- Upon completion of antibiotic-based eradication therapy for gastric EMZL, the panel recommends the following surveillance:
  - Urea breath test or *H. pylori* monoclonal stool antigen at least 6 weeks after starting eradication therapy and at least 2 weeks after cessation of PPI.
  - Tumour response should be confirmed by repeat gastroscopy 3 months later.
  - If true CR, gastroscopy every 6 months for 2 years, then every 12–18 months. Duration of follow-up is not well defined and should be determined on a case-by-case basis.
  - If asymptomatic residual lymphoma (macroscopically or microscopically), gastroscopy every 3–6 months.
- For ocular adnexal EMZL with minimal symptoms, a trial of antibiotic-based eradication therapy may be considered. Those with poor response or with significant symptoms should be managed with ISRT (IV, B).
- For localised EMZL, ISRT (24–30 Gy) is a curative treatment associated with high rates of disease control, low toxicity rates and excellent OS of 95% at 5 years (II, B).
- Patients with HCV-related MZL and no indications for urgent cytoreductive therapy may undergo HCV treatment first (IV, B).
- Asymptomatic, advanced-stage EMZL may be monitored (IV, B).
- Several CIT regimens are available for symptomatic advanced EMZL (III, A).
- Ultra-low-dose RT (4 Gy in two fractions) achieves high response rates with minimal toxicity and is an effective palliative treatment (II, B).
- Site-specific clinical assessment and imaging are used to monitor response.

Splenic MZL

Asymptomatic patients with SMZL can be managed with active monitoring.[10,45] Indications for therapy include progressive splenomegaly and/or lymphadenopathy, constitutional symptoms, significant cytopenias that are not attributable to autoimmunity and refractory autoimmune cytopenias.

In patients with HCV infection, antiviral therapy is associated with a lymphoma response rate of 65%.[73,76,77] Upfront rituximab monotherapy (e.g. 375 mg/m^2 once per week for 4–8 weeks) is associated with an ORR of 92%, including a complete/suspected CR rate of 65%.[46,78] Rituximab maintenance over 1–2 years improves 5- year PFS (79% vs 52%).[78,79] Splenectomy results in rapid resolution of SMZL-related cytopenias in nearly all patients and an improvement of SMZL-related lymphocytosis in most. The median PFS after splenectomy is 8 years and 40–50% of patients may never require retreatment.[80–83] Although there are no randomised studies comparing splenectomy with rituximab as a first-line therapy for SMZL, a large real-world data study demonstrated similar OS and event-free survival.[46] In accordance with Spleen Australia guidelines,[84–86] antimicrobial prophylaxis and vaccines should be delivered before these therapies if possible.

Upfront CIT may be considered in patients with substantial, symptomatic extrasplenic disease. Six cycles of BR is associated with an ORR of 91–96%, a CR rate of 73–86% and a 3-year PFS of 90%.[87,88] It may be associated with longer PFS than R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine and prednisone), acknowledging that PFS differences were not statistically significant within the MZL subgroups of the seminal StiL NHL1 and BRIGHT trials. The phase 2 BRISMA/IELSG36 study demonstrated similarly encouraging efficacy of BR in SMZL.[87] The very favourable PFS can be prolonged by maintenance but needs to be balanced against the risk of infection, impaired response to vaccines and hypogammaglobulinaemia.[89] In addition to the Lugano criteria, SMZL-specific criteria have been proposed, with CR defined as resolution of splenomegaly, normalisation of blood cell counts and undetectable lymphoma cells on peripheral blood flow cytometry and bone marrow immunohistochemistry.[31,90]

Recommendations

- For asymptomatic patients, we recommend active monitoring 3–6 monthly initially, and thereafter every 12–18 months (III, B).
- We recommend rituximab monotherapy as the first line of therapy for most patients with SMZL (III, A).
- For patients with symptomatic splenomegaly and no contraindication to surgery, splenectomy also remains a reasonable first-line clinical option (III, A).
- For patients with SMZL and symptomatic nodal involvement, BR can be considered a first-line option (III, B).

• Either rituximab monotherapy or BR chemotherapy may be followed by 2-monthly maintenance with rituximab for 1–2 years with the goal of prolonging PFS, but this needs to be balanced against the risk of infection (III, B).
• Antimicrobial prophylaxis and vaccines should be delivered before these therapies if possible (III,B).

Nodal MZL

Studies in NMZL are limited and therapeutic strategies are often derived from follicular NHL. For patients with stage I/II NMZL, curative-intent ISRT is the recommended standard of care. Doses of 24–30 Gy (in 1.5–2 Gy per fraction) achieve an excellent durable local progression-free rate of 90% at 5 years.[91,92] In the FORT (Fear of Cancer Recurrence Therapy) randomised control trial, ultra-low-dose RT (4 Gy in two fractions) was associated with a modest decrease in disease control (70% local progression-free rate at 5 years)[91]; however, it is exceptionally well tolerated and convenient to deliver, and may offer valuable palliative benefits for patients with advanced stage disease or those in whom durable local control is not the primary aim of therapy. The guiding principles of ISRT are published by ILROG to aid uniformity of RT in clinical practice.[92]

For asymptomatic patients with advanced-stage NMZL, adoption of a 'watchful waiting' approach is recommended. Systemic therapy may be considered for patients with advanced-stage NMZL that is symptomatic or demonstrates an increasing disease tempo; however, the optimal first-line regimen is yet to be defined. Various regimens have been trialled, including BR, R-CHOP, R-CVP and fludarabine, rituximab with or without cyclophosphamide (Table 4). In two large randomised trials, when comparing BR with R-CHOP, patients with MZL achieved similar ORRs and rates of CR and PFS (57 vs 47 months; hazard ratio: 0.70, 95% confidence interval: 0.34–1.43).[93,94] Obinutuzumab-based regimens do not offer better efficacy and are associated with higher rates of adverse events.[95] Alternate regimens demonstrating efficacy include chlorambucil-rituximab.[74] Evidence to support rituximab maintenance is derived from studies in other subtypes of MZL with improvement in PFS but not OS.[96] Single-agent rituximab is reserved for patients where frailty or comorbidities make them a poor candidate for CIT.[79]

HCV eradication may be appropriate in patients with minimal symptoms.[76,97]

The majority of paediatric nodal MZL cases in children and adolescents are treated with complete resection followed by observation, with excellent outcomes observed.[98,99]

Recommendations

• For patients with limited-stage NMZL, ISRT (24–30 Gy) given with curative intent is recommended over observation (III, C).
• Patients with asymptomatic, advanced nodal MZL may be safely observed but require close follow-up (IV, C).

Table 4 CIT regimens in NMZL

Study	Treatment	Median duration of follow-up	Progression-free survival	Overall survival
Rummel *et al*. 2013[94]	R-CHOP 3-weekly for up to six cycles ($n = 253$) versus BR 4-weekly for up to six cycles ($n = 261$)	45 months	R-CHOP: 31.2 months (15.2–65.7) BR: 69.5 months (26.1 to not reached) HR: 0.58; 95% CI: 0.44–0.74; $P < 0.0001$	Not assessed
Flinn *et al*. 2019[93]	BR 4-weekly for up to six cycles ($n = 224$) versus R-CHOP ($n = 104$) or R-CVP ($n = 119$) 3-weekly for up to six cycles	65 months	At 5 years: BR: 65.5% R-CHOP/R-CVP: 55.8 HR: 0.61; 95% CI: 0.45–0.85; $P = 0.0025$	At 5 years: BR: 81.7% R-CHOP/R-CVP: 85% HR: 1.15; 95% CI: 0.72–1.84; $P = 0.5461$
Herold *et al*. 2022[95]	G-chemotherapy ($n = 99$) versus R-chemotherapy ($n = 96$) for six cycles; chemotherapy = BR, R-CVP or R-CHOP	59.3 months	At 4 years: G-chemotherapy: 72.6% R-chemotherapy: 64.1% HR: 0.79; 95% CI: 0.47–1.31; $P = 0.35$	At 4 years: G-chemotherapy: 81.8% R-chemotherapy: 78.1% HR: 0.82; 95% CI: 0.44–1.51; $P = 0.52$

BR, bendamustine plus rituximab; CI, confidence interval; CIT, chemoimmunotherapy; FCR, fludarabine, cyclophosphamide plus rituximab; G, obinutuzumab; HR, hazard ratio; NMZL, nodal marginal zone lymphoma; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine plus prednisone; R-CVP, rituximab, cyclophosphamide, vincristine plus prednisolone.

- Patients with symptomatic, advanced nodal MZL are treated with CIT with appropriate regimens, including BR, R-CHOP and R-CVP (II, B).
- Single-agent rituximab is reserved for patients with significant comorbidities or frailty (III, C).
- Ultra-low doses of RT (4 Gy in two fractions) offer excellent palliative benefits for patients with symptomatic sites of disease (I, A).
- Response assessment with contrast-enhanced CT should be performed at the end of therapy.

R/R MZL and future directions

The treatment of relapsed/refractory (R/R) MZL is contingent upon: (i) the response to the initial therapy, (ii) the stage at relapse and (iii) the clinical and pathobiological features of the disease. Patients with aggressive or rapidly progressive disease should be carefully evaluated for the presence of transformation to an aggressive histology.

Targeted therapies were not reimbursed in Australia or New Zealand at the time of this consensus statement. Several novel agents are currently under investigation for MZL, so participation in a clinical trial should be strongly considered. The genomic landscape of MZL presents molecular targets that are subject to investigation with small molecule inhibitors. Most advanced of these are Bruton tyrosine kinase (BTK) inhibitors, with ibrutinib achieving Food and Drug Administration approval for treatment of relapsed MZL.[100] c studies, exploring the role of zanubrutinib and acalabrutinib in relapsed MZL respectively, confirmed the class effect of this approach.[101,102] Importantly, correlative translational data from these studies have provided insight into predictors of response and acquired resistance.[103–105]

Lenalidomide plus rituximab (R^2) has demonstrated improved efficacy over rituximab monotherapy in the phase III AUGMENT study in R/R MZL though numbers were small.[106] R^2 is a reasonable option for patients with <2 years remission to rituximab-based CIT. Although it is currently not reimbursed in Australia or New Zealand for this indication, generic brand availability may make it more accessible.

Responses have been observed in small numbers treated with CAR-T cells and bispecific antibodies such as blinatumomab, glofitamab, epcoritamab and mosunetuzumab.[107–109] Other options include PI3K,[110] ibritumomab tiuxetan[111] and BCL-2 inhibitors.[112]

In the absence of a clinical trial, it is recommended to start CIT in those who have not received it as first-line therapy or to repeat (including rituximab monotherapy) provided the initial response was adequate, for example, at least 2 years treatment-free response.[79] Autologous stem cell transplant may play a role in select young, fit patients with chemosensitive relapses, though the evidence is limited.[113] Splenectomy may provide long-term responses in patients with SMZL.[114]

Recommendations

- Patients with aggressive or rapidly progressive disease should be investigated for transformation.
- Relapsed MZL is often amenable to further RT, if tissue tolerance allows (IV, C).
- Late SMZL relapses can be retreated with rituximab monotherapy (III, B).
- In the absence of a suitable clinical study, CIT can be repeated if the treatment-free response is at least 2 years (III, B).
- For patients with early relapse or refractory disease, novel therapies are preferred, if available (III, B).
- Patients with SMZL and splenomegaly-related symptoms, should be considered for splenectomy as an alternative to rituximab (IV, B).
- Novel agents, including BTK inhibitors and lenalidomide, are promising but not readily available (III, B).

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Supplemental Table 1. Levels of evidence.
Supplemental Table 2. Grades of recommendation.