Summary

1) MZL comprises several different and relatively uncommon disease entities within the WHO classification including, roughly in decreasing order of frequency:-

   a) Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM)
   b) Extranodal MZL (MALT) lymphoma
   c) Splenic MZL (splenic lymphoma with villous lymphocytes)
   d) Nodal MZL (this is rare and needs to be differentiated clearly from Cyclin D1 negative mantle cell lymphoma)
   e) Hairy cell leukaemia has it’s own specific guidelines see EMCN Hairy Cell Leukaemia Guidelines

2) Each of these diseases is managed differently, although in all instances chemotherapy (with the possible exception of HCL) is palliative.

3) For the most part, these are relatively indolent diseases that can be observed for progression. Many patients may never require systemic therapy.

4) In part due to their relative rarity, there are few randomized clinical trials that speak to optimal therapy for any of these diseases and few/no relevant objective laboratory prognostic markers to guide choice of therapy and predict outcome.

Importantly, the role of rituximab in these diseases remains to be established unequivocally from RCTs. All of these malignancies express CD20 on the cell surface at much higher levels than CLL for example and, in some instances, patients may enter durable remissions with single agent MAb therapy alone. Given the lack of toxicity of rituximab many patients with MZL will receive rituximab at some stage in the course of their disease.

A major international study is to currently open that compares rituximab with obinutuxumab in nodal MZL (not Waldenstroms) patients – importantly, this study will also involve 2 years of maintenance therapy as per follicular lymphoma.

http://clinicaltrials.gov/ct2/show/NCT01332968

Enrolment into this study is encouraged.
These guidelines cover the two most common forms of MZL, namely Waldenström's macroglobulinemia and MALT lymphoma.

**Guidelines for the treatment of Waldenström macroglobulinemia**

Diagnosis of WM is not usually problematic.

WM most typically presents following the incidental finding of an IgM paraprotein.

More rarely, more advanced/aggressive forms may present with bone marrow failure, hyperviscosity with cold haemagglutinin disease or amyloidosis. These patients may often require immediate therapy.

**Investigations at diagnosis**

Most patients with WM present with a low-level IgM paraprotein with only low-level infiltration of, (or normal) bone marrow. Most patients do not exhibit significant organomegaly or lymphadenopathy; the development of lymphadenopathy during the course of the disease raises the possibility of transformation to DLBCL.

- Peripheral blood assessment – note that it may be necessary to collect samples warm if significant cold agglutinins are present.
- Full blood count, plasma viscosity
- Direct antiglobulin test.
- Renal and hepatic function tests
- LDH and β2M levels
- Immunology
  - paraprotein levels
  - cryocrit and cryoglobulin levels
  - C3 and C4 levels
- Bone marrow aspirate and trephine with immunophenotyping of lymphoplasmacytic cells
- CT scan chest abdomen and pelvis

Some patients with WM will have a positive family history of the disease. Such patients should be entered into the familial lymphoproliferative study which is anticipated to reopen shortly.

See [http://www.icr.ac.uk](http://www.icr.ac.uk)

**Principles of therapy of WM**

Patients who are asymptomatic should be observed. Treatment should not be based on paraprotein levels alone. In many instances, the slow progression of disease may allow GP monitoring.

Treatment is indicated by the development of one or more of the following complications:

- bone marrow failure
b) symptomatic hyperviscosity
c) severe neuropathy often due to anti-myelin associated glycoprotein (MAG) antibodies.
d) cold haemagglutinin disease
e) cryoglobulinemia/amyloidosis etc.

**Principles of systemic therapy of WM.**

The principles of therapy of WM are broadly similar to those of follicular lymphoma. Overall, aims of therapy are dictated by the condition of the patient and in particular suitability for high-dose chemotherapy and autologous stem cell transplantation (ASCT). Myelotoxic regimens should be avoided if ASCT is contemplated. All chemotherapy regimens are palliative. For the younger patients without significant comorbidities RIC allografts should be considered.

**First line therapy**

As with follicular lymphoma, there are no RCTs that aid the choice of first-line chemotherapy; there are for example, no RCTs demonstrating benefit from the addition of anthracyclines.

For fit patients in whom ASCT is considered many UK clinicians would use CVP as per follicular lymphoma. By analogy with follicular lymphoma many physicians would use rituximab in combination with CVP, although there are no data to show benefit of addition of rituximab to this regimen.

A German study however has shown that addition of rituximab to CHOP chemotherapy significantly improves remission rates and improved OS in a small cohort of WM patients (48 in total).

**Figure 1 – TTF in 48 patients with advanced WM treated with either CHOP or RCHOP. Buske C et al**.
A single European centre\(^2\) non-randomised comparison of response rates obtained with various cyclophosphamide/rituximab regimens showed the following overall response rates (ORR) and complete response (CR) rates to therapy as follows:-

- RCHOP (ORR, 96%; CR, 17%)
- RCVP (ORR 88%; CR 12%)
- RCP (ORR, 95%; CR, 0%)

The role of maintenance rituximab therapy in WM has not been established in the context of a RCT. However, a recent paper has documented increased PFS and OS with maintenance rituximab.

**Maintenance Rituximab is associated with improved clinical outcome in rituximab naïve patients with Waldenstrom Macroglobulinaemia who respond to a rituximab containing regimen.**

Diagram A –Progression Free Survival (PFS)

![Diagram A –Progression Free Survival (PFS)](image)

Diagram B –Overall Survival (OS)

![Diagram B –Overall Survival (OS)](image)

Reference\(^3\)

**Recommendations for first line therapy**

1. **RCVP** - recommended as treatment of choice for the majority of first-line patients with WM requiring therapy. 6 to 8 cycles should be administered according to response as per the follicular lymphoma protocols.

Bone marrow aspirate and trephine should be taken at the end of therapy to assess response.
CT scan may also be indicated depending on the presence of nodal disease/splenomegaly at diagnosis.

Other options in patients considered unfit for RCVP due to comorbidities include:-

2. **Chlorambucil** - single agent (see CLL protocol)

or

3. **Melphalan +/- prednisolone** – (see myeloma protocol)

Three additional WM-specific conditions also need to be considered:-

4. **Pancytopaenic patients**
Some patients requiring therapy may be severely pancytopenic due to heavy bone marrow infiltration. In such patients consider administering single agent rituximab (4 doses of 375mg/m² on a weekly basis) in order to improve blood counts prior to more definitive chemotherapy to avoid protracted infections. Data on a cohort of 30 patients thus treated have been presented⁴.

5. **Symptomatic hyperviscosity**
In patients with symptomatic hyperviscosity the aim is to bring down the levels of the paraprotein rapidly to prevent complications. Daily plasmapharesis may be required to bring down the plasma viscosity. Rituximab should not be administered until after completion of planned plasmapharesis!

6. **Treatment of anti-MAG antibody-mediated polyneuropathy.**
Antibody-mediated complications may arise in the absence of bulk disease and may require treatment. Many patients will develop a predominantly sensory polyneuropathy. A recent RCT comparing rituximab (at regular lymphoma doses of 375mg/m² weekly for 4 weeks) to placebo has shown that about 50% of patients with anti-MAG antibody induced neuropathy may make a durable response to rituximab.

Treatment with rituximab should be administered in collaboration with a neurologist in order to monitor responses objectively⁵.

Patients with WM receiving rituximab should be observed for the so-called “flare” reaction, representing an increase in the serum IgM levels due to rapid tumour cell death. This is well documented in the literature.

There are currently no data from RCTs to indicate that maintenance rituximab has a role in the “plateau” phase of WM although by analogy with follicular lymphoma this is likely and efficacy would be relatively easy to assess in WM.

### Second line therapy

Complete remissions in WM following any form of induction chemotherapy are uncommon and in most studies the median time to progression is relatively short, in the order of 30 months. Most patients will therefore require further systemic therapy within 5 years of initial treatment. The aim for most patients with relapsed disease will be to obtain a sufficiently good second remission in order to progress to ASCT.
Younger patients without significant comorbidities may be considered for Reduced Intensity Chemotherapy (RIC) allogeneic stem cell transplantation in first or second remission; allografting in first remission should be considered for younger patients due to the poor outcomes with conventional chemotherapy.

There is no consensus about how best to treat relapsed disease; the following algorithm is taken from a recent review.

One salvage regimen is fludarabine-based, often Fludarabine Mitoxantrone Dexamethasone (FMD) in patients lacking co-morbidities but this will preclude subsequent stem cell harvesting due to the myelotoxicity.

Therefore, consider harvest the stem cells from cyclophosphamide priming before commencing definitive chemotherapy.

Avoid “rainy day” harvests due to wastage of stem cells.

Data from European Bone Marrow Transplant (EBMT) on 202 WM patients, most of whom had relapsed or refractory disease, showed a 5-year progression-free and overall survival rates after ASCT were 33% and 61%, respectively.

Chemosensitive disease at time of the ASCT was the most important prognostic factor for overall survival in this series.
Guidelines for the Treatment of MALT

Gastric extranodal MALT lymphoma

MALT lymphomas comprise about 7% of all lymphomas. They can arise at any anatomical location but most involve stomach and/or lungs. These guidelines will refer principally to gastric MALT lymphoma but the similar principles can be applied to patients presenting with disease at other sites.

Diagnosis of gastric MALT lymphoma

Most patients with gastric MALT lymphoma present with non-specific upper gastrointestinal symptoms. Upper GI endoscopy usually shows gastritis.

Biopsies should be taken from all areas of the stomach on repeat endoscopy once the diagnosis has been determined to establish the extent of disease.

Presentation with ulceration and/or with mass lesions is unusual and might raise the possibility of transformation to DLBCL.

Diagnosis is based on the histopathological evaluation of gastric biopsies.

BCL10 nuclear expression and/or the presence of t(11;18)(q23;q21) chromosomal translocation should be sought to identify prospectively patients unlikely to respond to antibiotic therapy.

If the presence of active *Helicobacter pylori* infection is not demonstrated by histochemistry it must be ruled out by urea breath test and/or faecal antigen test.

Investigations at diagnosis

- Full blood count
- Direct antiglobulin test
- Renal and hepatic function tests, LDH and β2M levels
- Immunology – paraprotein levels and autoimmune profile
- Bone marrow aspirate and trephine
- CT scan: chest abdomen and pelvis (PET scanning appears to have little role in this disease)
- Gastric dilation procedures should be used to visualize disease adequately.

Principles of Therapy

Recommendations for first line therapy

Eradication of *H. pylori* with antibiotics +/- proton pump inhibitors should be employed as the sole initial treatment of localized *H. pylori*-positive gastric MALT lymphoma as per BNF guidelines.

*H. pylori* eradication can induce lymphoma regression and long term clinical disease control in most *H. pylori* –positive patients. The length of time necessary to induce
remission can be up to 12 months. Monoclonal B-cells can persist in follow up biopsies in the absence of histological evidence of disease.

On occasion *H. pylori* NEGATIVE cases can respond clinically to antibiotic therapy and should be prescribed with monitoring.

Patients with associated lymph nodal disease are much less likely to respond to antibiotic eradication than those with disease confined to the gastric mucosa.

### Recommendations for second line therapy

For patients who fail to respond to simple medical treatment with persistent symptoms and/or progressive disease +/- mess lesions there are a variety of therapeutic options and the choice of approach will depend on the patient’s overall condition. The therapeutic options include:

1. Gastric irradiation
2. Single agent chlorambucil
3. Combination chemotherapy – RCVP as per follicular lymphoma guidelines

The role of maintenance therapy in this disease has yet to be established and should not be given outside of a clinical trial.

Transformation to DLBCL should be considered in resistant cases.

### Rarer subtypes of MZL

**a) Nodal marginal zone lymphoma.**

Nodal MZL (NMZL) is a rare form of nodal lymphoma. It should only be diagnosed in the absence of extranodal MZL.

It is a diagnosis of exclusion, which can only really be sustained from an excision lymph node biopsy. NMZL cells are mature B cells that express CD20, CD79a, and IgM, but lack expression CD5, CD23, and cyclin D1, and lack the expression germinal center markers CD10 and BCL6.

The principles of treatment are as for follicular lymphoma.

There are no specific RCTs for NMZL. For patients requiring systemic therapy, R-CVP or single agent chlorambucil are recommended depending on overall clinical condition.

A clinical trial (Gallium) is currently open for these patients.

**b) Splenic marginal zone lymphoma/Splenic lymphoma with villous lymphocytes.**

These two conditions overlap and are likely to be identical. The hallmark clinically is splenomegaly, often associated with the presence of characteristic lymphocytes with villous projections in the peripheral blood. An IgM paraprotein is often present. Unlike hairy cell leukaemia, CD25 and CD103 are not expressed. Bone marrow infiltration may be modest, even in the presence of massive splenomegaly.
Cytogenetics may show chromosomal translocations involving the CDK6 gene with the IG loci.

Most patients are asymptomatic and do not require therapy. Splenectomy may be indicated in patients with progressive disease and/or cytopenias.

Only rarely do these patients require systemic therapy. Most are elderly and have significant comorbidities and therefore single agent chlorambucil may be appropriate.

One single center report of 16 patients has documented extremely high activity of single agent rituximab in this disease, although the dosing scheme used in this study was not conventional and maintenance therapy was given to a subset of patients (6).
References


