MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG) TO THE MYELOMA FOUNDATION OF AUSTRALIA (MFA)

Clinical Practice Guideline

WALDENSTRÖM MACROGLOBULINAEMIA

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Myeloma Australia

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TREATMENT OF PATIENTS WITH WALDENSTRÖM MACROGLOBULINAEMIA

Clinical practice guidelines from the Myeloma Foundation of Australia Medical and Scientific Advisory Group

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1 INTRODUCTION

Waldenström Macroglobulinaemia (WM) is a B-cell lymphoid malignancywhich is defined by the World Health Organization (WHO) as a disease manifested by a monoclonal IgM paraprotein and infiltration of the bone marrow (BM) by clonal small B lymphocytes, plasmacytoid lymphocytes and plasma cells[1,2]. It constitutes less than 5% of all NHLs, with an incidence of ≈0.3/100,000 cases/year[3]. The recent discovery of the MYD88 L265P mutation in >90% WM patients[4], and the advent of newer treatments such as bendamustine and rituximab[5], and ibrutinib[6] have changed the diagnostic and therapeutic landscape of the disease.

The clinical practice guideline for the treatment of WM is a consensus established by the Australian Medical Scientific Advisory Group (MSAG) to the Myeloma Foundation Australia (MFA), which consists of a panel of haematologists across Australia, as well as local experts. Levels of evidence and grades of recommendations in this guideline are as shown in **table 1**. Statements without grading were considered justified standard clinical practice by the panel and the experts.

Table 1 Level of evidence and grades of recommendations.

LEVELS OF EVIDENCE	
1A	Evidence from meta-analysis of randomised control trials
1B	Evidence from at least one randomised controlled trial.
2A	Evidence from at least one well-designed non-randomised trial, including phase II trials and case-control studies
2B	Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies.
3	Evidence from well-designed non-experimental descriptive studies.
4	Evidence obtained from expert committee reports or opinions and/or of respected authorities.
GRADES OF RECOMMENDATION	
A	Recommendation based on at least randomised controlled trial of good quality addressing specific recommendation (evidence level 1A and 1B)
B	Recommendation based on well-conducted studies but no randomised controlled trial on topic of recommendation. (Evidence level 2A, 2B, and 3)
C	Recommendation based on expert opinions or reports (Evidence level 4)

2 DIAGNOSTIC CRITERIA

There is no minimal amount of BM infiltration or threshold concentration of monoclonal IgM required for the diagnosis. The WHO defines IgM monoclonal gammopathy of undetermined significance (MGUS) as a small monoclonal IgM protein associated with a clone of lymphoplasmacytic cells not detectable morphologically in the bone marrow, that may progress into lymphoplasmacytic lymphoma/ Waldenström Macroglobulinaemia[1,2]. The Mayo Clinic diagnostic criteria for WM require at least 10% BM infiltration, and define the entity of IgM MGUS as being characterised by an IgM paraprotein of < 30 g/L, BM involvement of <10% and absence of anaemia, hyperviscosity, constitutional symptoms, lymphadenopathy or organomegaly[7]. Asymptomatic (smouldering) WM is diagnosed when there are no symptoms requiring treatment **(Table 2)**[8].

2.1 COMMON PRESENTATIONS

Most patients with WM present with signs and symptoms related to the monoclonal IgM protein and/or to tumour infiltration. The large sized pentameric IgM protein causes hyperviscosity symptoms in up to 15% of patients such as blurred vision, dizziness, headache, confusion and haemorrhagic symptoms[9]. Anaemia and thrombocytopenia are common and are associated with BM infiltration or autoimmunity. Unlike other lymphomas, only 20% of patients present with lymphadenopathy and/or organomegaly; some patients may present with B symptoms. Other less common manifestations include neuropathy, cryoglobulinemia, skin rash (occasionally as a manifestation of Schnitzler syndrome[10]), cold-agglutinin haemolytic anaemia, and amyloidosis [11] **(Table 2)**. The Bing Neel syndrome is a rare complication associated with central nervous system infiltration with lymphoplasmacytoid and plasma cells and resultant variable neurological symptoms[12,13]. Approximately 25% patients will have a family history of WM and/or other non-Hodgkin lymphomas (NHL)[14].

Table 2: The Spectrum of IgM Gammopathy, and Treatment Indications

Feature	IgM-Monoclonal Gammopathy of Undetermined Significance (MGUS)	Asymptomatic Waldenström Macroglobulinaemia (WM)[87]	Symptomatic WM	Treatment Indication
IgM paraprotein	≤ 30g/L No hyperviscosity	Any level; >30g/L if paraprotein is sole criterion No hyperviscosity		1. Asymptomatic and >60g/L [11] or 2. Symptomatic hyperviscosity*
Bone marrow	Not infiltrated (<10% as per Mayo criteria)	Clonal lymphoplasma-cytic cells	Clonal lymphoplasmacytic cells	
Cytopenias	Absent	Absent	May be present	Haemoglobin < 100 g/L Neutrophils < 1.0 x 10^9/L Platelet <100 x 10^9/L
Spleen, lymph node, other tissues	Absent	Absent	May be present	Symptomatic organomegaly Bulky (>5 cm) and/or symptomatic lymphadenopathy Symptomatic infiltration of other tissues
Disease-related symptoms	Absent	Absent	May be present - cytopenias - B symptoms - neuropathy - cryoglobulinemia - cold agglutinin haemolytic anaemia - skin rash - nephropathy (Paraproteinemia associated diseases with end organ damage)	Immune haemolytic anaemia or thrombocytopenia Fever, night sweats, weight loss or fatigue Peripheral neuropathy Nephrotic syndrome Amyloidosis Symptomatic cryoglobulinemia
MYD88 L265P Mutation	Present in 50% High risk of WM if present	Present in > 90%	Present in > 90%	

*Note the relationship between IgM paraprotein levels and symptoms is not linear.

2.2 DIAGNOSTIC WORKUP

The recommended investigations for suspected WM are listed in **Table 3.** The minimum criteria of IgM paraprotein and BM infiltration require serum protein electrophoretic studies, and a BM biopsy. A BM aspirate and trephine are required to differentiate between IgM MGUS and WM. However, it can be difficult to determine the monoclonal protein threshold at which a BM biopsy is indicated, especially in asymptomatic patients. In a large cohort of 213 patients with monoclonal IgM, patients with an IgM paraprotein of ≤ 10g/L had a 10 year progression rate of 14%, compared with 26 – 41% 10-year progression rate for higher paraprotein values (Kyle 2003:3759). Therefore, a reasonable threshold and our recommendation for withholding a BM aspirate and trephine in asymptomatic patients is a paraprotein of <10g/L. **(Table 3).** As IgM levels do not correlate well with the amount of lymphomatous infiltration, BM is also recommended in symptomatic patients with clinical evidence of 'end-organ' dysfunction particularly if treatment is likely to be considered.

Table 3: Recommended Workup for WM

GROUP	TEST	INDICATED IN / COMMENTS
History and examination	Clinical assessment of hyperviscosity symptoms and signs, including fundoscopy and neurological exam, Lymphadenopathy, organomegaly, skin rash. Urine dipstick for proteinuria Family history of WM/NHL	All patients
Blood and urine tests	Full blood count and blood film Urea & electrolytes, calcium, phosphate, uric acid Liver function tests LDH and ß2-microglobulin Iron studies Serum electrophoresis (SPEP) and serum immunoglobulins PT, aPTT Urine protein *HIV, *hepatitis B (including core antibody) * Hepatitis C serology Markers of haemolysis (retics, LDH and haptoglobin) Direct Coomb's test Cryoglobulin screen only where indicated (skin rash etc) Plasma viscosity	All patients IgM measurement by SPEP and nephelometry may vary substantially[25] Hep B status important for rituximab therapy Hep C status important for cryoglobulinemia
Bone marrow	BM aspirate and trephine Flow cytometry Perl's stain for iron stores Molecular study for MYD88 L265P mutation	Patients with paraprotein >10g/L or WM related symptoms
Radiology	*CT neck/chest/abdomen/pelvis with contrast	Patients with clinical lymphadenopathy and proven WM
Advanced prognostic tests	Sequencing for CXCR4 mutations Marrow cytogenetics	May provide additional prognostic value, where available.

*These tests do not need performing at diagnosis, and can be performed prior to treatment.

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Table 3: Recommended Workup for WM …continued

SPECIAL SITUATIONS		
Suspected amyloidosis	ECG, echocardiogram, troponin and BNP; consider cardiac MRI and biopsy Serum free light chains 24 hour urine for proteinuria and Bence Jones protein Congo red staining on BM Organ specific biopsy	Patients suspected to have amyloidosis
Neuropathy	Neuronal antibody screen (anti-MAG, anti-GM1, anti-sulfatide IgM) Nerve conduction studies	Patients with peripheral neuropathy suspected to be related to WM
Bing Neel syndrome	MRI brain CSF sampling for cytology, flow cytometry, protein and glucose	Patients with features of possible direct central nervous system involvement (Bing-Neel syndrome)
Haemorrhagic disease	PT, aPTT Factor studies, vWD studies, platelet aggregation.	Patients with bleeding history

Bone Marrow:

The characteristic BM appearance in WM is that of diffuse interstitial and/or nodular infiltration with plasmacytoid lymphocytes, small lymphocytes and plasma cells[1] (**Figure 1**).

BM assessments in WM require additional testing including inmmunophenotyping. On flow cytometry, the cells are light chain restricted, express B cells markers (CD19, CD20, dim CD22), are positive for CD25 and usually lack expression of CD5 and CD10[15]. Immunohistochemical analysis with CD20 may help quantify the infiltrate and distinguish between IgM MGUS and WM. In contrast to myeloma, the clonal plasma cell population shows normal antigen expression on flow cytometry and immunohistochemistry[16].

Other investigations such as assessment of iron stores (Perl stain), and screening for amyloid deposition (Congo red) should be performed, the latter if clinically indicated.

Emerging evidence that the MYD88 L265P mutation is present in >90% of WM has meant that molecular testing for the mutation is being increasingly used in the diagnosis of WM[4]. This has led to its inclusion in the diagnostic criteria for WM in the 2016 revision of the World Health Organisation classification of lymphoid disorders[17]. Alternative diagnoses should be considered in patients negative for the MYD88 mutation. WM patients without MYD88 L265P are reported to have more aggressive and treatment-resistant disease[6,18]. Approximately 50% of patients with IgM MGUS are positive for MYD88 L265P, and have a significantly increased risk of progression to WM[19].

Less commonly accepted tests on BM include cytogenetics and CXCR4 mutational testing. The most common cytogenetic abnormality in WM is deletion of 6q, present in 40 – 90% patients[20]. This is often mutually exclusive with CXCR4 mutations, which are present in ~30% patients with WM[21]. CXCR4 mutations may be associated with resistance to chemotherapy and Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib[22,23].

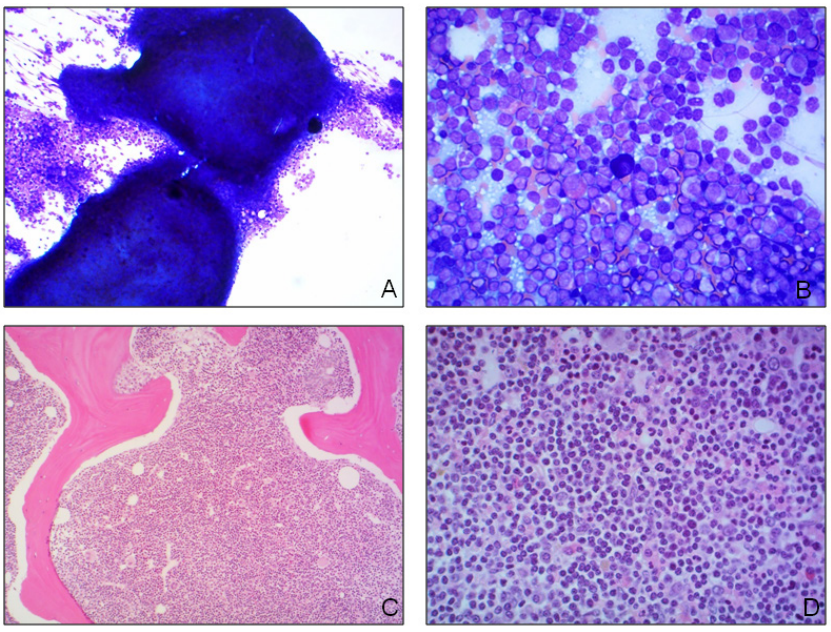

Figure 1: Bone marrow findings in Waldenström Macroglobulinaemia

Panels A and B show a hypercellular bone marrow aspirate with a prominent infiltrate of small mature lymphocytes and lymphoplasmacytoid cells. A mast cell is seen in panel B; these are often increased in WM. Panels C and D shows a similar infiltrate on the trephine biopsy.

Protein studies: Serum protein studies include serum electrophoresis, immunofixation and serum immunoglobulin levels. Serum free light chains are not required routinely. One note of caution relates to the tendency of IgM paraproteins in some patients with cryoglobulinemia, to precipitate out of solution at room temperature, resulting in underestimation of paraprotein. If there is suspicion regarding the reliability of paraprotein testing in a given patient, a repeat sample transported at 37°C should be tested. Further, IgM can show variation in protein stability and aggregation that can affect serum electrophoresis results[24]. Where feasible, a second method such as IgM nephelometry is recommended, especially for difficult cases including those with multiple IgM peaks or peaks in the ß region[25].

Other investigations:

Where available, plasma viscosity can be a useful adjunct in the diagnostic work up of WM patients and is measured by the time required for plasma to flow through a tube under the influence of gravity. The inherent lack of precision and reproducibility can be overcome by reporting the time as a ratio to the time required for water to traverse the tube, especially in a given patient over time[26]. The test is not routinely available in all centres and the diagnosis of hyperviscosity remains a clinical one.

Patients with clinical lymphadenopathy should undergo CT scanning to assess the burden of nodal and splenic disease. PET scans, although not reimbursable, can be performed in patients with nodal disease.

Those with clinical features suggestive of amyloidosis, peripheral neuropathy and central nervous system infiltration (Bing-Neel syndrome) require further directed investigations **(Table 3).**

Some patients with WM have functional iron deficiency due to hepcidin excess, and their anaemia may improve with intravenous iron infusion even in the presence of detectable marrow iron stores[27,28].

Box 1: Workup of Suspected WM

- *All patients should have measurement of total IgM and serum electrophoresis with immunofixation; underestimation of the paraprotein level can occur when tested at room temperature, particularly in patients with cryoglobulinemia (Level III, grade C).*
- *BM aspirate and trephine should be performed in those with paraprotein ≥ 10g/L, or those with symptoms suggestive of WM at any level of paraprotein (Table 1) (Level III, grade C).*
- *MYD88 L265P mutation is a unifying test in the diagnosis of WM, and has been included in the diagnostic criteria for WM in the revised 2016 World Health Organisation classification of lymphoid neoplasms. The mutation is seen in > 90% of WM and in ~50% of IgM MGUS. At the time of marrow examination, MYD88 L265P mutation testing should be performed as far as possible (Level III, grade C).*
- *CT scan of the neck/chest/abdomen/pelvis is recommended in patients with clinical evidence of nodal involvement and splenomegaly prior to commencing treatment (Level IV, grade C).*

3 DIFFERENTIAL DIAGNOSIS:

A number of other mature B cell lymphoproliferative disorders can overlap with WM. The distinguishing features of these conditions are listed in **Table 4**.

Some patients with WM have functional iron deficiency due to hepcidin excess, and their anaemia may improve with intravenous iron infusion even in the presence of detectable marrow iron stores[27,28].

Table 4: Differential diagnosis of WM:

	DIFFERENTIATING FEATURES FROM WM
Splenic marginal zone lymphoma (SMZL)	Splenomegaly is more common, cells show polar villi, immunophenotype varies (higher CD22 and CD11c, less CD25 and CD103), cytogenetics is variable (7q, +3q, +5q), MYD88 only in 10%
Mantle cell lymphoma (MCL)	Nodal and extra nodal sites are common, inmmunophenotyping shows CD5+, CD23-, CD200- clonal B-cells). Characterised by t(11;14).
Follicular lymphoma (FL)	Nodal presentation, characterised by cleaved lymphocytes, CD10+ clonal B-cells, and t(14;18).
Small lymphocytic lymphoma	Nodal presentation, small lymphocytes, CD5+, CD23+, CD200+ immunophenotype

Prognostic Markers:

An International Scoring System for Waldenström Macroglobulinaemia (ISSWM) has been developed, based on 5 factors (age >65 years, haemoglobin (Hb) ≤ 115g/L, platelet count ≤ 100 x 10^9/L, ß2-microglobulin >3mg/L, paraprotein >70g/L)[29]. The ISSWM has been validated to predict survival [30,31], but does not impact on the decision to commence therapy, or on the choice of induction regimen.

4 TREATMENT OF WM: GENERAL COMMENTS

Patients with Hb level < 100 g/L or platelet count < 100 x 10^9/L attributable to WM, bulky adenopathy or organomegaly, symptomatic hyperviscosity, moderate to severe or advancing peripheral neuropathy, amyloidosis, cryoglobulinemia, nephropathy or cold-agglutinin disease are candidates for treatment **(Table 2).** Asymptomatic patients should have their IgM levels monitored serially and those with rapidly rising levels or with with IgM > 60 g/L should be considered for treatment to avoid hyperviscosity related complications [11] .

Before discussing specific therapeutic regimens in WM, it is important to recognize two important management aspects unique to WM.

1. Rituximab induced IgM flare
2. Response monitoring

4.1 Rituximab-Induced IgM Flare:

The use of rituximab in WM can be associated with a transient paradoxical rise in IgM – the so-called "IgM flare"[32,33]. This phenomenon is particularly common in patients receiving rituximab monotherapy (>25% rise in IgM reported in 26-73%)[2,33], and usually occurs in the first 8 weeks of initiating therapy. Awareness of this phenomenon is important as (1) serious hyperviscosity complications can occur during IgM flare, including intracerebral bleeding, and some patients may require urgent plasmapheresis for the treatment of this complication[32]; (2) neuropathy may acutely worsen[34]; and (3) IgM flare does not represent therapeutic failure, and an elevation of IgM in the first three months of starting a rituximab containing regimen should not be regarded as progressive disease without other features of disease progression. Some experts advocate withholding rituximab until the IgM falls below 40g/L, or treating with plasmapheresis before commencing rituximab[11].

4.1.1 Monitoring pre and post treatment and response assessment:

WM presents unique challenges in monitoring of the disease during the asymptomatic phase, and post treatment in the assessment of response due to

(1) Unreliability of IgM / paraprotein measurements in individual patients especially those with cryoglobulins, and;

(2) The lack of correlation between disease burden (as assessed by BM and CT evaluations) and changes in clinical situation i.e. disease progression or disease response post treatment – as assessed by changes in symptoms, haemoglobin and IgM levels. It is important to be aware that post treatment, reduction in IgM levels may be delayed for months to years in some responders.

Whether serial readings of the monoclonal paraprotein (as determined by serum electrophoresis and densitometry) or total IgM (as measured by nephelometry) should be followed during the asymptomatic phase prior to treatment, and for response assessment after treatment is debatable – the unique IgM monoclonal protein can be difficult to measure in individual patients due to technical factors[35,36]. We recommend both methods be assessed at first diagnosis, prior to commencement of treatment, and at confirmation of final response. One of the two methods should be used consistently for monitoring during the asymptomatic phase, and during treatment. The tests should preferably be performed in the same laboratory to provide reliable serial readouts.

The International Workshop on Waldenström Macroglobulinaemia (IWWM) has published response categories based mainly on IgM responses[37]: complete response (CR) requires a normal IgM level and complete absence of paraprotein by immunofixation; very good partial response (VGPR) and partial response (PR) represent ≥90%, and ≥50% but <90% fall in IgM from baseline, respectively, with detectable monoclonal IgM; minor response (MR) is ≥25% and <50% fall in IgM from baseline. In addition, CR requires complete resolution of extramedullary disease (e.g. lymphadenopathy and splenomegaly), and morphological clearance of the BM **(Table 5).**

Another special feature in the management of WM is the not uncommon occurrence of delayed paraprotein responses which can occur months to years after cessation of therapy[38,39]. Therefore, it is important to follow IgM levels with patience after completion of therapy, and not regard persistent raised IgM as a sign of therapy resistance, particularly if there are other indications of therapeutic response such as a rise in haemoglobin levels, BM clearance and/or resolution of symptoms. There is no consensus on the timing of response assessments including BM; it is recommended that this be determined on an individual basis and be directed by clinical assessment, specifically resolution of symptoms and anaemia.

Table 5: International Workshop on Waldenstrom's Macroglobulinaemia (IWMM) response criteria

	PROTEIN STUDIES	BONE MARROW	EXTRAMEDULLARY DISEASE
Complete Response (CR)	Normal IgM level and complete absence of paraprotein by immunofixation	Morphological clearance	Complete resolution of lymphadenopathy and organomegaly
Very Good Partial Response (VGPR)	>90% fall in IgM levels from baseline		reduction in extra medullary sites of disease
Partial Response (PR)	>50 but < 90% fall in IgM levels from baseline		reduction in extra medullary sites of disease
Minor response (MR)	≥25% and <50% fall in IgM from baseline		reduction in extra medullary sites of disease
Stable Disease (SD)	<25% fall in IgM from baseline		

4.1.2 Drug access in Australia

An important practice point for Australian clinicians is the access to Pharmaceutical Benefits Scheme (PBS) subsidised drugs for the treatment of WM. Bendamustine has recently been approved on the PBS for *first line* treatment of indolent NHL (iNHL) but is not reimbursed for patients with relapsed or refractory disease. Clinicians should be aware of this limitation when planning a treatment strategy for patients with WM. Rituximab has been PBS listed for the relapsed or refractory setting and access has been recently expanded for CD20 positive low grade lymphomas in the frontline setting. Bortezomib and ibrutinib are not yet available on PBS for the treatment of WM. Therefore, treatment recommendations in Australia differ from those of international guidelines (Supplementary Appendix A), with a reduced emphasis on bortezomib, ibrutinib and other newer agents. Although an adequately powered, randomised study of rituximab inclusion in frontline induction of WM is lacking, the collective favourable outcomes of rituximab in combination with chemotherapy in the treatment of other B-cell malignancies has led to its inclusion as frontline therapy in these guidelines (grade C recommendation, level III-3 evidence). Due to the relative paucity of randomised controlled trials in WM, it is strongly recommended that patients be enrolled in clinical trials – cross referrals to tertiary centres with trial availability should be considered.

5 FRONTLINE THERAPY OF WM

Therapy should be offered only for symptomatic disease or when disease-related complications are present **(Table 2).** There is no single accepted standard frontline regimen for WM. Within the current Australian regulatory environment, the most pragmatic regimens, depending on the age, presence of co-morbidities and general fitness of the patient, are bendamustine and rituximab (B-R), or dexamethasone, rituximab and cyclophosphamide (DRC) for transplant eligible candidates. Transplant ineligible patients may additionally be treated with a fludarabine-based regimen (e.g. FCR, fludarabine, cyclophosphamide and rituximab, or FR). Chlorambucil may an appropriate regimen for the frail and/or elderly. Doses and schedules of B-R, DRC, FCR, FR, and single agent chlorambucil and rituximab are listed in **Table 6.**

Bendamustine-Rituximab (B-R):

The large randomised study comparing bendamustine and rituximab with R-CHOP in 549 indolent and mantle cell lymphomas included 41 patients (22: B-R arm, 19: R-CHOP arm) with lymphoplasmacytic lymphoma/ Waldenstrom Macroglobulinaemia. A significant improvement in progression free survival (PFS) was noted in the B-R arm vs. the R-CHOP arm across all histological subtypes including WM (69.5 months vs. 28.1 months, HR 0.33, CI 0.11-0.64, p=0.0033)[5]. Further, a preliminary analysis on the B-R induction arm of the randomised controlled trial on Rituximab maintenance vs. observation in WM showed an overall response rate (ORR) of 86%[40]. As Bendamustine and Rituximab are both now PBS-approved, B-R is the preferred first line therapy for WM.

Dexamethasone, Rituximab and Cyclophosphamide (DRC)

While there are no randomised controlled trial data, DRC was assessed in a Greek Myeloma Study Group phase II study of 72 frontline patients. ORR of 74% (7% CR) was obtained and an additional 9% had minor response (MR)[41,42] **(Supplementary Table 1).** The median PFS was 35 months, and median overall survival (OS) was 95 months. The regimen was well tolerated with grade ≥3 neutropenia and thrombocytopenia rates of 9% and 0%, respectively. The long duration to response is one disadvantage of DRC (median time to partial response 4.1 months), and thus this regimen may not be suitable where rapid control of IgM is desired. On the other hand, the regimen is not stem cell toxic and is unlikely to impair haematopoietic stem cell mobilisation.

Chlorambucil and R-CHOP Regimens

Phase II and III experiences of single-agent chlorambucil as initial therapy of WM reported response rates of 39 – 75%, median PFS of 26 – 46 months, and a 3 – 9% risk of myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)[43,44].

Two randomised studies evaluating frontline CHOP vs. R-CHOP (GLSG)[45] and R-CHOP vs. R-bendamustine (B-R) (StiL)[5] included subgroups of patients with WM **(Supplementary Table 1).** Although the response rate of R-CHOP was high at 91-95%, the reported median PFS varied greatly between the two studies, being 63 months in the GLSG study[45], and 28 months in the StiL study [5]. The comparatively favourable performance of B-R in the StiL study (ORR 95%, median PFS 70 months, p=0.003) compared with R-CHOP has led to a recommendation against the use of R-CHOP in WM.

Fludarabine-Based Induction Regimens

Fludarabine use in WM is supported by phase III evidence[44,46]. In the frontline setting, the randomised WM1 study showed that fludarabine had better response rates and PFS than chlorambucil with ORR for fludarabine of 48%, and median PFS of 36 months **(Supplementary Table 1)**[44]. Phase II studies of fludarabine or the alternative purine analogue cladribine also showed ORR of 38 – 85%, and prolonged median PFS of up to 60 months **(Supplementary Table 1)**[47,48]

The addition of rituximab to fludarabine, cladribine or fludarabine + cyclophosphamide (FC) has been tested in phase II studies, and has produced very high response rates of ≥ 90% and prolonged median PFS of > 51 months **(Supplementary Table 1)**[49-51].

However, fludarabine-based regimens are associated with increased toxicity in older patients (> 65 years) and in those with impaired renal function (GFR < 70ml/min), in whom dose reduction should be considered. Additionally, fludarabine is associated with stem cell toxicity and failure to mobilise stem cells in WM and chronic lymphocytic leukaemia (CLL)[52,53], and should be avoided in young patients who are potential future candidates for autologous stem cell transplantation (ASCT). Finally, a retrospective series reported an increased risk of disease transformation and MDS associated with fludarabine treatment of WM[54]. Although this observation was not supported by other patient series including the prospective WM1 study **(Table 6),** the potential concern for MDS/AML has led some physicians to favour FR (avoiding cyclophosphamide) over FCR. Cladribine has also been observed to be associated with large cell transformation[55]. Because of these reasons and the availability of other regimens with lower toxicity, it is recommended that this regimen be avoided or used with caution for frontline treatment.

Bortezomib and Carfilzomib

A number of studies using proteasome inhibitors have been conducted in WM **(Supplementary Table 1)**[56-59]. In general, combinations of proteasome inhibitors and rituximab achieve ORR of 65 – 83%, and median PFS of 2 to 4 years, somewhat inferior to those seen with fludarabine- or bendamustine-based regimens. Their advantages include rapid paraprotein response which may be particularly beneficial in patients with hyperviscosity syndrome, IgM levels, renal disease and amyloidosis; lack of stem cell toxicity, and reduced risk of MDS. Further, bortezomib has been reported to be particularly beneficial in patients with familial disease[14]. However, bortezomib can exacerbate WM-related neuropathy, with reported grade 3-4 neuropathy rates of 20 - 30% when given twice-weekly and intravenously[56,58,60,61]. This risk may be reduced by administering bortezomib weekly[57,62], or by the use of the second-generation proteasome inhibitor carfilzomib[59]. There are no data on the use of subcutaneous bortezomib in WM but this can be considered based on the data in myeloma patients. These drugs are not registered or funded for treatment of WM in Australia.

Rituximab as single agent and as Maintenance

Rituximab has been trialled as a single agent in 27 patients (15 untreated, 12 pre-treated) with responses noted in 40% of untreated and 50% of pre-treated patients. The median time to response was 3.3 months and the median time to progression for all patients was 16 months. Treatment was well tolerated although infusional reactions were noted in 25% of cases[63].

While maintenance rituximab is routine in the treatment of follicular lymphoma[64], and there are observational data to support its use in rituximab responsive patients in WM[65], randomised studies to support this practice are lacking. There are no studies that define the risk of infection with rituximab maintenance in WM; a phenomenon that is known to be important in maintenance rituximab therapy for CLL. Rituximab maintenance therapy is not available through the PBS currently and is not recommended as routine practice at this point in time.

BOX 2: INITIAL THERAPY OF WM

- *Treatment should only be given for symptomatic WM meeting therapy criteria (Table 1) (Level III, grade C), or in those with asymptomatic but very high IgM (>60g/L) (Level IV, grade C).*
- *Patients should be enrolled in clinical trials wherever possible.*
- *Reasonable first-line regimens for WM include B-R, which is superior to R-CHOP with reduced toxicity (Level IB, grade A) and DRC ((level III, grade B)*
- *Fludarabine-based regimen such as FCR or FR are effective (Level II, grade B) but may be associated with increased toxicity in older patients and those with impaired renal function, may impact on stem cell mobilisation, and may increase the risk of MDS / AML. For these reasons, fludarabine should be avoided or used with caution in frontline treatment (Level III, grade C).*
- *Chlorambucil has been shown to have poorer response rates, PFS and OS compared to fludarabine (Level I, Grade A). Single agent rituximab produces responses in up to 50% with low toxicity (Level 2, Grade B). There may be a role for single agent treatment in elderly and/or frail patients who cannot tolerate other treatments (Level IV, grade C).*
- *There is little efficacy gained with the use of anthracycline and vincristine in R-CHOP. This regimen is not recommended for treatment of WM as B-R is more efficacious and less toxic (Level IB, grade A).*
- *Patients receiving rituximab may develop an IgM flare for ~8 weeks and caution should be exercised in assessment of response (Level II, grade B).*
- *Proteasome inhibitors such as bortezomib may be useful in rapid lowering of paraprotein especially in patients with hyperviscosity symptoms and in patients with familial WM (Level III, grade C).*

Table 6: Doses and Schedules of Frontline Regimens for WM

REGIMEN	DOSE AND SCHEDULE	COMMENT
B-R[5]	Bendamustine 90 mg/m2 Days 1, 2 Rituximab 375mg/m2 iv D1 28 day cycles X 6	Steroid sparing regimen, Due to risk of IgM flare, consider withholding rituximab until paraprotein levels are <40g/L. Patients who are elderly and/ or have poor performance status tolerate this regimen well. In these patients, and in those with renal failure, dose of Bendamustine can be reduced to 70 mg/m2 and/or number of cycles reduced to 4.
DRC[41]	Dexamethasone 20mg iv D1 Rituximab 375mg/m2 iv D1 Cyclophosphamide 100mg/m2 oral twice daily D1 – 5 (total dose over 5 days 1000 mg/m2) 3 weekly cycles x 6	Not stem cell toxic. Due to risk of IgM flare, consider withholding rituximab until paraprotein levels are <40g/L
FR[49,88]	*Fludarabine 25mg/m2 iv D1 – 5 Rituximab 375mg/m2 iv D1 28 day cycles x 6 *Fludarabine can also be administered orally at a dose of 40mg/m2.	Stem cell toxic. Due to risk of IgM flare, consider withholding rituximab until paraprotein levels are <40g/L. Consider dose reduction in patients over the age of 65 years, and those with GFR <70ml/min.
FCR[51,88]	*Fludarabine 25mg/m2 iv D1 – 3 Cyclophosphamide 250mg/m2 iv D1 – 3 Rituximab 375mg/m2 iv D1 4 weekly cycles x 6 *Fludarabine can also be administered orally at a dose of 40mg/m2.	Stem cell toxic. Due to risk of IgM flare, consider withholding rituximab until paraprotein levels are <40g/L. Consider dose reduction in patients over the age of 65 years, and those with GFR <70ml/ min. May carry increased MDS risk relative to FR.
Chlorambucil[88]	Chlorambucil 8 mg/m2 PO D1-10 28 day cycles X 12 (max)	In frail and/or elderly Risk of MDS/AML
Rituximab – single agent[63]	Rituximab 375 mg/m2 IV D1 4 doses at weekly intervals	Should be avoided in patients with high IgM because of risk of “IgM flare”. May be useful in patients with poor performance status unable to tolerate chemotherapy, and in patients with autoimmune complications.

Supplementary Table 1: Overview of Published Regimens for the Treatment of WM

Regimen (N)	N	Overall Response (%)	Median Progression Free Survival	AML/ MDS	Median overall survival (OS)	Comments
FRONTLINE STUDIES						
Bendamustine + Rituximab[5] Bendamustine + Rituximab[40]	22 116	95% 86%	70 months -	<1% -	- -	
Rituximab, cyclophosphamide, dexamethasone (DRC)[41]	72	74% (CR 7%)	35 months	1%	95 months	
Chlorambucil[43] (Mayo) Chlorambucil[88] (WM1)	46 209	64 - 75% 39%	26-46 mths 27 months	9% 3%	5.4 years 69.8 months	
Fludarabine[88] (WM1) Fludarabine[47] (SWOG) Cladribine[48]	209 118 26	48% 38% (CR 3%) 85% (CR 12%)	36 months 60 months NR	0.5% NR NR	Not reached 5yr OS 62% -	
Fludarabine + Rituximab[49] Cladribine + Rituximab[70] FC + Rituximab[51]	27 16 28	89% (CR 4%) 94% 93% (CR 15%)	77 months 65+ months 51+ months	4% 0% 0%	- - -	
R-CHOP (GLSG)[45] R-CHOP[5](StiL 1-2003)	23 19	91% (CR 9%) 95%	63 months 28 months	NR <1%	- -	
Bortezomib (NCIC)[56]	27	25%	16 months	NR	-	
Bortezomib + Rituximab[57] Bortezomib + Dexa + Ritux[58] Bortezomib + Dexa + Ritux[62]	26 23 59	65% (CR 4%) 83% (CR 13%) 68% (CR 3%)	12+ months 30+ months 42 months	NR NR NR	- - 3yr OS 81%	0% PN ; 30% PN; 7% PN
Carfilzomib + Dexa + Ritux[59]	31	68% (CR 3%)	55% at 2 yr	NR	-	
RELAPSED/ REFRACTORY STUDIES						
Bendamustine + various[66] Bendamustine + Rituximab[71]	30 13	83% (CR 0%) NR	13 months 32 months	3% NR	- =	
Cyclophosphamide, adriamycin, prednisolone[46]	45	11%	3 months	4%	41 months	
Fludarabine (Phase 3)[46] Fludarabine (SWOG)[47] Cladribine[48]	45 64 46	30% 33% (CR 0%) 43%	19 months 30% at 5y 12 months	9% NR NR	45 months 5yr OS 50% -	
Fludarabine + Rituximab[49] Fludarabine + Various[68] FC + Rituximab[69] Cladribine + Rituximab[50]	20 19 40 13	81% (CR 5%) 74% 80% (CR 10%) 85%	38 months 36 months 77 months > 65 months	10% 16% 5% 0%	- - - -	
Bortezomib (Greek)[60] Bortezomib (WMCTG)[61] Bortezomib (NCIC)[56]	10 27 15	60% (CR 0%) 48% (CR 0%) 27% (CR 0%)	NR 7 months 16 months	NR NR NR	- - -	20% G3 PN; 22% G3 PN; 19% G3 PN
Bortezomib + Rituximab[72] Bortezomib + Rituximab[73]	37 10	52% 90%	17 months NR	NR NR	- -	
Ibrutinib[6]	63	73% (CR 0%)	24+ months	NR	2yr OS 95%	

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Supplementary Table 1: Overview of Published Regimens for the Treatment of WM… continued

Regimen (N)	N	Overall Response (%)	Median Progression Free Survival	AML/ MDS	Median overall survival (OS)	Comments
AUTOLOGOUS STEM CELL TRANSPLANTATION						
Consolidation of 1st response[76] Consolidation of 1st response[77]	12 69	100% (CR17%) NR	69 months 60 months	NR NR	Not reached -	Subset population
All disease stages[89] All disease stages[77]	10 158	NR NR	36+ months 48 months	NR 4%	3yr OS 70% 5yr OS: 68.5%	NRM 11%; NRM 5.6%
ALLOGENEIC STEM CELL TRANSPLANTATION						
Allogeneic SCT[90] Myeloablative conditioning (MAC) Reduced intensity conditioning (RIC)	MAC: 37 RIC: 49	ORR 75.6%	MAC: 56% at 3 yr RIC: 49% at 3 yr		MAC: 62% at 3 yrs RIC: 64% at 3 yr	MAC: 33% at 3 yr RIC: 23% at 3 yrs

6 TREATMENT OF RELAPSED WM

There is no standard treatment for relapsed WM and the options depend on (1) quality and duration of first response, (2) patient fitness and tolerance of therapy, (3) whether the patient is a candidate for ASCT, (4) availability of novel agents, and (5) whether there is unresolved toxicity from previous therapies such as neuropathy or myelosuppression. Published results of relapsed WM therapy are summarized in **Supplementary Table 1**.

Generally speaking, the Eighth International Workshop on WM (IWWM-8)[66] recommends that any of the front-line regimens can be used for re-treatment provided the patient has maintained a response for > 2 years. The only significant randomised controlled study in the setting of relapsed WM is the French CAP (cyclophosphamide, adriamycin and prednisolone) vs. fludarabine study[46]. In this study, patients salvaged with CAP had poor ORR and a short median PFS of only 3 months, suggesting that an adriamycin-containing, CHOP-like regimen is likely an inferior choice. In contrast, the results of fludarabine-based or bendamustine-based regimens are superior, with median PFS of 12 to 36 months particularly when combined with rituximab[11,66-70]

(Supplementary Table 1). A multicentre open-label phase 3 randomised study in patients with relapsed indolent lymphomas included 24 patients with WM with a median age of 67 years. The study showed improved PFS overall with B-R compared to Fludarabine and Rituximab (34.2 months vs. 11.7 months, HR = 0.54, p<0.0001)[71]. Subgroup analysis of the WM cohort showed a median PFS of 32 months for the B-R arm vs. 12 months for the F-R arm. In the United States, bortezomib-based regimens are commonly used in the salvage setting, producing median remission durations of approximately 12 – 18 months[56,60,61,72,73].

Ibrutinib:

Most recently, the United States Food and Drug Administration (FDA) licensed the BTK inhibitor ibrutinib for the treatment of WM, based on a phase II study[6]. In this study, ibrutinib achieved an ORR of 73% (no CRs) in patients with relapsed or refractory WM, with the major toxicities being bleeding, an increased risk of atrial fibrillation and gastrointestinal side effects. The 2-year PFS is currently 69%[6]. Clinical trials in the frontline setting are ongoing. Patients who have received Ibrutinib and progressed on treatment should not be re-treated with Ibrutinib.

Other novel agents:

There are a number of novel agents being trialled in WM patients. Upregulation of the protein kinase C (PKC) beta, and PI3/mTOR pathways is known and has led to the use of enzastaurin (PKC beta inhibitor) and rapamycin (mTOR inhibitor) in WM with variable success[74]. Lenalidomide is associated with prolonged anaemia in some patients at standard doses[74] but does of 15mg/day of lenalidomide have been shown to be safe and efficacious[75].

Stem Cell Transplantation

ASCT should be considered as a potential treatment option in younger patients with relapsed or refractory WM. Two small studies have reported on the role of frontline ASCT in WM[76,77]. Prolonged median PFS of 60 months or more were reported, but these results are not sufficiently superior to those of modern induction regimens such as DRC to justify the cost and toxicity **(Supplementary Table 1)**. ASCT is therefore not recommended in the frontline setting. In the relapsed setting, retrospective studies have reported median PFS of 3 – 4 years across a variety of disease stages[77,78]. Younger patients with good physical fitness should be considered for ASCT at first or second relapse, and particularly before the administration of stem cell toxic therapies such as fludarabine (Level III, grade B). Feasibility of stem cell mobilisation after bendamustine therapy has not been studied in the setting of WM. However, retrospective data in myeloma patients has shown that adequate numbers of stem cells can be successfully mobilized and engraftment obtained in patients pre-treated with bendamustine[79].

Allogeneic stem cell transplantation is reserved for younger, fit patients with relapsed or refractory disease who have a suitable donor.

Supportive care

Emergent management of symptomatic hyperviscosity at diagnosis or during treatment (to prevent IgM flare in patients with IgM levels > 40 g/L planned for Rituximab therapy) requires plasmapheresis to remove the large IgM pentamer[80]. Avoidance of red cell transfusions is recommended in this setting; if absolutely necessary, this should be timed to follow plasmapheresis[81] with careful fluid management to prevent exacerbation of hyperviscosity and acute pulmonary oedema. Iron infusions may be useful for management of functional iron deficiency secondary to hepcidin excess[28]. The sensorimotor neuropathy of WM can be partially reversed with rituximab based therapy in some patients[82,83]. Management of neuropathy should be undertaken in conjunction with a neurologist and treatment with pregabalin may be required for symptomatic relief. The presence of nephropathy often requires careful dieresis and fluid management due to extra vascular fluid in consultation with a renal physician. Treatment of WM can be complicated by infections, especially in patients with hypogammaglobulinaemia, and while there is lack of specific data in patients with WM, anti-microbial, anti-viral and anti-fungal prophylaxis is recommended for those who develop recurrent or life-threatening infections, and/or are receiving intensive or immunosuppressive therapy.

Transformation to large cell disease

Histological transformation to diffuse large B-cell lymphoma (DLBCL) is known to occur in 5-10% of patients, especially those who have received nucleoside analogues[55,84] and is characterised by rapidly enlarging lymphadenopathy or extranodal disease, and rising lactate dehydrogenase. A tissue biopsy is recommended to confirm histological transformation, and tested for EBV as it has been implicated in the pathogenesis,[85,86]. PET scan may be particularly useful in the diagnosis of large cell transformation. There is lack of specific data on outcomes in patients with transformed disease. It is recommended that these patients be treated with intensive chemotherapy regimens similar to those used for de-novo DLBCL. Responsive and fit patients may be considered for autologous and/or allogeneic transplantation. Palliation can be achieved through less intensive approaches including radiotherapy and high dose steroids.

BOX 3: TREATMENT OF RELAPSED WM

- *Patients with indolent relapse of WM (e.g. biochemical relapse without symptoms or end-organ effects) can be observed without active therapy (Level IV, grade C).*
- *Consideration should be given to enrolling patients on clinical trials, particularly if previous chemotherapy responses are short (<12 months) (Level IV, grade C). .*
- *Patients should not be re-exposed to the same regimen if the previous response is less than 12 months (Level IV, grade C).*
- *Younger patients with good physical fitness should be considered for autologous and allogeneic stem cell transplantation at first or second relapse, and should avoid stem cell toxic therapies such as fludarabine (Level III, grade C).*
- *Patients with persistent myelosuppression (e.g. hypocellular marrow and thrombocytopenia) should avoid fludarabine (Level II, grade B); conversely, patients with unresolved neuropathy should avoid bortezomib (Level II, grade B).*

7 CONCLUDING REMARKS

WM is no longer an orphan disease treated with therapies borrowed from indolent lymphomas and multiple myeloma. Improved understanding of WM biology including recognition of MYD88 L265P as a primary driver has led to the development of targeted therapies such as the BTK inhibitors. At the same time, unique aspects of WM management such as rituximab-induced IgM flare pose challenges to less experienced clinicians and underscore the need for disease-specific treatment guidelines. Given the rapid advances in WM therapy and the relatively poor access to novel drugs in Australia, enrolment of patients into WM-specific clinical trials is strongly encouraged.

Supplementary Appendix A: International Consensus Statements on Treatment of WM

Two main international consensus statements on the therapy of WM exist: one from the IWWM[66], the second from the National Comprehensive Cancer Network (NCCN)[92].

The IWWM guidelines emphasize the following principles:

(1) Recommended first-line regimens were (a) B-R (bendamustine and rituximab), (b) DRC (dexamethasone, rituximab, and cyclophosphamide), or (c) bortezomib, rituximab and dexamethasone;

(2) Rituximab maintenance is not recommended due to current paucity of evidence;

(3) R-CHOP and fludarabine-based regimens were specifically recommended against in frontline;

(4) Salvage therapy after remissions of ≥12 months may include repeat administration of the induction regimen;

(5) Salvage options after shorter remissions include switching to a different chemotherapy – or bortezomib-based regimen (including fludarabine combinations), ASCT, or a biological agent such as the BTK inhibitor ibrutinib, ofatumumab or carfilzomib. Of note, ibrutinib has recently received FDA and EMEA approval for treatment of WM.

The major difference between the IWWM guidelines and Australian practice is the lack of public funding for bortezomib and ibrutinib for treatment of WM in Australia.

The NCCN guidelines are similar to the IWWM guidelines, with an increased emphasis on bortezomib-based or DRC induction due to lack of stem cell toxicity and perceived reduced rates of second cancers, compared with B-R or fludarabine-based regimens. The NCCN guidelines also recommend routine testing of serum viscosity in WM, with levels of ≥4cP being associated with hyperviscosity complications. This test is not universally available in Australia, where judgments regarding severity of hyperviscosity manifestations were commonly made on clinical features.

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