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POSITION PAPER

Treatment of patients with Waldenström macroglobulinaemia: clinical practice update from the Myeloma Foundation of Australia Medical and Scientific Advisory Group

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Key words
Waldenström macroglobulinaemia, treatment, Bruton tyrosine kinase inhibitor.

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Abstract

Waldenström macroglobulinaemia (WM) is an indolent B-cell malignancy characterised by the presence of IgM paraprotein, bone marrow infiltration by clonal small B lymphocytes with plasmacytic differentiation and the MYD88 L265P mutation in >90% of cases. Traditionally, WM has been treated with chemoimmunotherapy. Recent trials have demonstrated the efficacy and safety of Bruton tyrosine kinase inhibitors in WM, both as monotherapy and in combination with other drugs. There is emerging evidence on the use of other agents including B-cell lymphoma 2 inhibitors and on the treatment of rare presentations of WM. In this update, the Medical and Scientific Advisory Group of Myeloma Australia reviews the available evidence on the treatment of WM since the last publication in 2017 and provides specific recommendations to assist Australian clinicians in the management of this disease.

Introduction

Waldenström macroglobulinaemia (WM) is a B-cell malignancy characterised by monoclonal IgM paraprotein and infiltration of the bone marrow (BM) by clonal small B lymphocytes, plasmacytoid lymphocytes and plasma cells.[1] The advent of Brutons tyrosine kinase inhibitors (BTKis) has changed the therapeutic landscape of the disease.

This update to the previously published clinical practice guideline for the treatment of WM[2] is from the Medical and Scientific Advisory Group of Myeloma Australia. The full form of the guideline is reported separately.[3]

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Treatment of WM: general comments

IgM monoclonal gammopathy of undetermined significance and asymptomatic WM, which precede symptomatic disease, do not usually warrant therapy; treatment indications for WM are listed in Table 1.

The recommended workup of patients with WM has been previously published[4] (Table 2**)**.

Approved treatment regimens for therapy in Australia

The chemoimmunotherapy regimens approved for use in WM through the Pharmaceutical Benefits Scheme (PBS)

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Table 1 The spectrum of IgM gammopathy and treatment indications[2]

Feature	IgM-Monoclonal gammopathy of undetermined significance	Asymptomatic WM[20]	Symptomatic WM	Treatment indication
IgM paraprotein	≤30 g/L No hyperviscosity	Any level; >30 g/L if paraprotein is the sole criterion No hyperviscosity		**1** Asymptomatic and >60 g/L or **2** Symptomatic hyperviscosity†
Bone marrow	Not infiltrated (<10% as per Mayo criteria)	Clonal lymphoplasmacytic cells	Clonal lymphoplasmacytic cells	
Cytopenias	Absent	Absent	May be present	Haemoglobin <100 g/L Neutrophils <1.0 × 10^9/L Platelet <100 × 10^9/L
Spleen, lymph node and 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 – cryoglobulinaemia – cold agglutinin haemolytic anaemia – skin rash – nephropathy (Paraproteinaemia associated diseases with end-organ damage)	Immune haemolytic anaemia or thrombocytopenia Fever, night sweats, weight loss or fatigue Peripheral neuropathy Nephrotic syndrome Amyloidosis Symptomatic cryoglobulinaemia
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.
WM, Waldenström macroglobulinaemia.

in Australia are bendamustine-rituximab (B-R) and dexamethasone-rituximab-cyclophosphamide (DRC). B-R is publicly funded only for frontline treatment.

Zanubrutinib is the only BTKi currently reimbursed through PBS in Australia. Ibrutinib and zanubrutinib are covered in this guideline. Acalabrutinib and tirabrutinib are covered in the full guideline.[3]

Please refer to previous guidelines for details on other chemoimmunotherapy regimens.[2]

Management aspects unique to WM

IgM flare or rebound

A rapid >25% rise in IgM levels called 'IgM flare' or 'IgM rebound' is seen after rituximab monotherapy and after cessation or interruption of BTKis. The former term is used with rituximab monotherapy and the latter with BTKis.

This phenomenon was reported in 73% of patients either on cessation or interruption of ibrutinib after surgery, with approximately half occurring within the first 4 weeks. About half, ie, 46%, return to preibrutinib levels. IgM rebound can persist for several months following reinitiation of therapy, and persistent elevation of IgM in this setting does not represent treatment failure. If in doubt, continuing BTKis with regular monitoring of symptoms and IgM levels is recommended. Rarely, temporary treatment with plasmapheresis is required for hyperviscosity. Short-course low-dose prednisolone can be used for systemic symptoms such as fever, fatigue, myalgia and arthralgia.

Monitoring pretreatment and posttreatment and response assessment

Patients with WM require monitoring of IgM during the asymptomatic phase and posttreatment for response assessment. We recommend measurement of total IgM and IgM paraprotein at first diagnosis, before commencement of

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Table 2 Recommended workup for WM[2,4]

Group	Test	Indicated in/comments
History and examination	Clinical assessment of hyperviscosity symptoms and signs, including a fundoscopy and neurological examination, lymphadenopathy, organomegaly and skin rash	All patients
	Urine dipstick for proteinuria	
	Family history of WM/NHL	
Blood and urine tests	Full blood cell count and blood film	All patients
	Urea and electrolytes, calcium, phosphate and uric acid	IgM measurement by SPEP and nephelometry may vary substantially
	Liver function tests	
	LDH and β2-microglobulin	Hepatitis B status important for rituximab therapy
	Iron studies	Hepatitis C status important for cryoglobulinaemia
	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 test	
	Cryoglobulin screen only where indicated (skin rash, etc.)	
	Plasma viscosity	
BM	BM aspirate and trephine	Patients with paraprotein >10 g/L or WM-related symptoms
	Flow cytometry	
	Perl stain for iron stores	
	Molecular study for MYD88 L265P mutation	
Radiology	CT† neck/chest/abdomen/pelvis with contrast	Patients with clinical lymphadenopathy and proven WM
Advanced prognostic tests	Sequencing for CXCR4 mutations	May provide additional prognostic value, where available
	Marrow cytogenetics	
Special situations		
Suspected amyloidosis	Echocardiogram, troponin and BNP; consider cardiac MRI and biopsy	Patients suspected to have amyloidosis
	Serum-free light chains	
	24-h urine for proteinuria and Bence Jones protein	
	Congo red staining on BM	
	Organ-specific biopsy	
Neuropathy	Neuronal antibody screen (anti-MAG, anti-GM1, anti-sulfatide IgM)	Patients with peripheral neuropathy suspected to be related to WM
	Nerve conduction studies	
Bing–Neel syndrome	MRI brain	Patients with features of possible direct central nervous system involvement (Bing–Neel syndrome)
	CSF sampling for cytology, flow cytometry, protein and glucose	
Haemorrhagic disease	PT, aPTT	Patients with a bleeding history
	Factor studies, vWD studies, platelet aggregation	

†These tests do not need performing at diagnosis and can be performed before treatment.
aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; CT, computed tomography; BM, bone marrow; BNP, B-type natriuretic peptide; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; PT, partial thromboplastin; SPEP, serum electrophoresis; vWD, von Willebrand disease; WM, Waldenström macroglobulinaemia.

treatment and at assessment of response. One of the two methods should be used consistently for monitoring, preferably at the same laboratory.

The International Workshop on Waldenström Macroglobulinaemia (IWWM) response categories based mainly on IgM responses are listed in Table 3.

Posttherapy drop/nadir in IgM levels may be delayed for months to years. It is crucial not to regard persistent raised IgM as a marker of therapy resistance in isolation from other indications of therapeutic response such as improved haemoglobin levels, BM clearance and/or resolution of symptoms.

There is no consensus on the timing or frequency of response assessments including BM; this should be individualised based on the resolution of symptoms and signs, especially anaemia.

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Table 3 International Workshop on WM response criteria

	Protein studies	Bone marrow	Extramedullary disease
Complete response	Normal IgM level and complete absence of paraprotein by immunofixation	Morphological clearance	Complete resolution of lymphadenopathy and organomegaly
Very good partial response	>90% fall in IgM levels from baseline		Reduction in extramedullary sites of disease
Partial response	>50% but <90% fall in IgM levels from baseline		Reduction in extramedullary sites of disease
Minor response	≥25% and <50% fall in IgM from baseline		Reduction in extramedullary sites of disease
Stable disease	<25% fall in IgM from baseline		

WM, Waldenström macroglobulinaemia.

Treatment options

Chemoimmunotherapy

For frontline therapy, B-R or DRC may be used depending on the age, comorbidities and general fitness of patients. There are no randomised data on the comparison of the two regimens. Treatment doses and schedules are listed in Table 4 and an overview of published regimens is listed in Table 5.

Bendamustine-rituximab

The randomised StiL (Study Group of Indolent Lymphomas) trial comparing B-R with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in 549 patients with indolent and mantle-cell lymphomas in the frontline setting included 41 patients (22: B-R arm and 19: R-CHOP arm) with WM. Progression-free survival (PFS) was better in the B-R arm versus the R-CHOP arm (69.5 vs 28.1 months, respectively; $P = 0.0033$).[5] This study is the basis on which R-CHOP is no longer recommended and B-R is a preferred first-line therapy for WM. Analysis of the B-R induction arm of the randomised controlled trial on rituximab maintenance versus observation in treatment-naïve (TN) patients with WM showed an overall response rate (ORR) of 86%.[6] Rituximab maintenance is not recommended in the treatment of WM.

A multicentre open-label phase III randomised study in patients with relapsed indolent lymphoma included 24 patients with WM and showed improved PFS on subgroup analysis in the WM cohort (32 months in the B-R arm vs 12 months in the F-R arm).[7]

Dexamethasone-rituximab-cyclophosphamide

DRC was assessed in a phase II study of 72 frontline patients. An ORR of 74% (7% CR) and 9% minor response were noted[8] (Table 5). The median PFS was 35 months and the median overall survival (OS) was 95 months. Treatment was well tolerated with grade ≥3 neutropenia and thrombocytopenia rates of 9% and 0%, respectively. The long median time to partial response of 4.1 months makes this regimen unsuitable when rapid control of IgM is desired. It may be the preferred regimen for frailer, older patients.

BTK inhibitor

The BTK signalling pathway is constitutively activated in WM, and activating mutations of MYD88, seen in >90% of patients with WM, provide further therapeutic rationale for BTK inhibition.

Ibrutinib

Ibrutinib, a first-in-class oral BTKi, was studied in the treatment of WM in a landmark phase II study.[9] Ibrutinib 420 mg achieved an ORR of 73% in 63 patients with relapsed/refractory (R/R) WM, with the major toxicities being bleeding, atrial fibrillation (AF) and gastrointestinal side effects. The 2-year PFS was 69%,[9] and the ORR and major response rates of 91% and 79%, respectively, were noted at a median follow-up of 59 months. Patients with mutated MYD88 and wild-type (WT) CXCR4 showed higher response rates and shorter times to response. The median PFS was 0.4 years in patients with mutated MYD88 and WT CXCR4, and 5-year PFS was 70% versus 38% for CXCR4 WT versus CXCR4 mutated cases, indicating poor efficacy in patients with mutated MYD88 and WT CXCR4s and in patients with double mutations (noting limitations of the small sample size).

The INNOVATE phase III randomised trial of rituximab + ibrutinib versus rituximab monotherapy of 150 symptomatic TN patients or patients with R/R WM showed a PFS of 82% at 30 months. Hypertension and AF at rates of 13% and 12%, respectively, and infusion-related reactions of 16% were noted.[10]

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Table 4 Doses and schedules of frontline regimens for WM

Regimen	Dose and Schedule	Comment
B-R	Bendamustine 90 mg/m^2 days 1 and 2 Rituximab 375 mg/m^2 IV day 1 28-day cycles × 6	Steroid-sparing regimen Because of the risk of IgM flare, consider withholding rituximab until paraprotein levels are <40 g/L
DRC	Dexamethasone 20 mg IV day 1 Rituximab 375 mg/m^2 IV day 1 Cyclophosphamide 100 mg/m^2 PO twice daily days 1–5 (total dose over 5 days 1000 mg/m^2) 3-weekly cycles × 6	Not stem cell toxic. Because of the risk of IgM flare, consider withholding rituximab until paraprotein levels are <40 g/L
Ibrutinib	420 mg OD	Limited to MYD88 mutated cases
Ibrutinib + rituximab	420 mg OD Rituximab 375 mg/m^2	Independent of MYD88 genotype
Zanubrutinib	160 mg BD or 320 mg OD PO	
IDR	Ixazomib PO 4 mg and Dexamethasone PO/IV 20 mg days 1, 8 and 15 Rituximab 375 mg/m^2 day 1 every 28 days	
FR	*Fludarabine 25 mg/m^2 IV days 1–5 Rituximab 375 mg/m^2 IV day 1 28-day cycles × 6 *Fludarabine can also be administered PO at a dose of 40 mg/m^2	Stem cell toxic. Because of the risk of IgM flare, consider withholding rituximab until paraprotein levels are <40 g/L. Consider dose reduction in patients older than 65 years and those with GFR <70 mL/min.
FCR	*Fludarabine 25 mg/m^2 IV days 1–3 Cyclophosphamide 250 mg/m^2 IV days 1–3 Rituximab 375 mg/m^2 IV day 1 4-weekly cycles × 6 *Fludarabine can also be administered PO at a dose of 40 mg/m^2	Stem cell toxic. Because of the risk of IgM flare, consider withholding rituximab until paraprotein levels are <40 g/L. Consider dose reduction in patients over the age of 65 years and those with GFR <70 mL/min. May carry increased MDS risk relative to FR.
Chlorambucil	Chlorambucil 8 mg/m^2 PO D1–10 28-day cycles × 12 (max)	In frail and/or elderly Risk of MDS/AML
Rituximab – single agent	Rituximab 375 mg/m^2 IV day 1 4 doses at weekly intervals	Should be avoided in patients with high IgM because of the risk of 'IgM flare'.

AML, acute myeloid leukemia; BD, twice a day; B-R, bendamustine-rituximab; DRC, dexamethasone-rituximab-cyclophosphamide; FCR, fludarabine-cyclophosphamide-rituximab; FR, fludarabine-rituximab; GFR, glomerular filtration rate; IDR, ixazomib-dexamethasone-rituximab; IV, intravenous; MDS, myelodysplastic syndrome; OD, right eye; PO, orally; WM, Waldenström macroglobulinaemia.

The study treated 31 rituximab-refractory patients with ibrutinib monotherapy, achieving an ORR of 90% and an 18-month PFS of 86%.[11] There is no direct comparison of ibrutinib versus ibrutinib-rituximab.

Zanubrutinib

Zanubrutinib is an oral second-generation BTKi with high selectivity for BTK.

The phase I/II study BGB-3111 AU-003 treated 77 BTKi-naïve patients with WM (24 TN and 53 R/R) with zanubrutinib 160 mg BD or 320 mg OD. At a median follow-up of 36 months for patients with R/R WM and 23.5 months for TN patients, the ORR was 95.9% and the very good partial response/complete response (VGPR/CR) rate was 45.2%. The VGPR rate increased from 20.5% at 6 months to 43.8% at 24 months. The estimated 3-year PFS rate was 80.5% and the OS rate was 84.8%.[12]

Reasons for treatment discontinuation included adverse events (13%), disease progression (10.4%) and other causes (3.9%).[12]

The phase III ASPEN study compared ibrutinib monotherapy ($n = 99$) with zanubrutinib ($n = 101$) in 201 symptomatic patients with mutated MYD88 and WM.[13] Results showed similar PFS at 18 months (84% and 85%), and a difference in VGPR of 19% versus 28% favouring zanubrutinib ($P = 0.09$). Adverse events including cardiovascular toxicity (AF and grade 3+ hypertension) and those resulting in discontinuation of treatment were less often seen with zanubrutinib. Neutropenia was more common with zanubrutinib, but infections of grade 3 or higher were similar at 1.2 and 1.1 per 100-person months.

As ibrutinib monotherapy was reported to have poor outcomes in WM patients with WT MYD88, the ASPEN study included a cohort of MYD88 negative/unknown patients.[14] Of the 28 patients included in the study (26 mutated MYD88 and WT CXCR4 and

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BOX 1 Frontline therapy of WM (adapted from Talaulikar *et al.*[2])

- Treatment should only be given for patients with symptomatic WM meeting therapy criteria (Table 1) (level III, grade C) or for those with asymptomatic but very high IgM (>60 g/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).
- *Zanubrutinib monotherapy is funded through PBS for frontline therapy in patients ineligible for chemoimmunotherapy and is effective irrespective of MYD88 genotype, with fewer off-target effects (level 1B, grade A).
- *Ibrutinib monotherapy is not funded through PBS but is effective in patients with MYD88 mutations (level 1B, grade A). In the MYD88 WT genotype, it is recommended that ibrutinib be combined with rituximab (level 1B, grade A).
- Fludarabine-based regimens such as fludarabine-cyclophosphamide-rituximab or fludarabine-rituximab are effective (level II, grade B) but are likely to be associated with increased toxicity in older patients and those with impaired renal function; may impact stem cell mobilisation and may increase the risk of myelodysplastic syndrome/acute myeloid leukemia. For these reasons, fludarabine should be avoided in frontline treatment (level III, grade C).
- Chlorambucil has been shown to have poorer response rates, PFS and OS compared with fludarabine (level I, grade A). It is therefore not recommended for treatment.
- Single-agent rituximab produces responses in up to 50% of cases 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 the treatment of WM as B-R is more effective and less toxic (level IB, grade A).
- Patients receiving rituximab, especially as a single agent, may develop an IgM flare for ~8 weeks and caution should be exercised in the assessment of response (level II, grade B).
- Proteasome inhibitors, such as bortezomib, may be useful in the rapid lowering of paraprotein, especially in patients with hyperviscosity symptoms and in patients with familial WM (level III, grade C).

**Please note at the time of publication of the manuscript, zanubrutinib is but ibrutinib is not funded by PBS for frontline treatment.*

two mutations unknown), 50% achieved a major response and 27% a VGPR. At 18 months, PFS and OS were 68% and 88%, respectively. This substudy established the efficacy of zanubrutinib monotherapy in patients with mutated MYD88 and WT CXCR4.

Treatment recommendations

Treatment recommendations for frontline and R/R WM are listed in Boxes 1 and 2. Levels of evidence and grades of recommendations are shown in Table 1.

BOX 2 Treatment of R/R WM (adapted from Talaulikar *et al.*[2])

- 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 enroling patients in 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).
- *Zanubrutinib monotherapy is approved through PBS and is effective irrespective of MYD88 genotype, with fewer off-target effects (level 1B, grade A).
- *Ibrutinib monotherapy is recommended if available in patients with MYD88 mutation (level 1B, grade A). In the MYD88 WT genotype, it is recommended that ibrutinib be combined with rituximab (level 1B, grade A).
- Younger patients with good physical fitness can 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).

**Please note at the time of publication of the manuscript, zanubrutinib is but ibrutinib is not funded by PBS for treatment.*

Noting that zanubrutinib is funded through the PBS, it is recommended as frontline therapy especially in those who are not candidates for chemoimmunotherapy because of age or comorbidities. Zanubrutinib monotherapy can be used in patients irrespective of MYD88 genotype, negating the need for testing. Ibrutinib monotherapy is an acceptable alternative in patients with mutated MYD88 but is not PBS-funded. It is not advised in patients with MYD88 and WT CXCR4; for such patients, an ibrutinib and rituximab regimen appears to have better efficacy.

In the absence of standard treatment for R/R WM, options depend on: (i) availability of novel agents, (ii) duration of first response, (iii) patient fitness and (iv) toxicity from previous therapy, i.e., neuropathy or myelosuppression. Published results of R/R WM therapy are summarised in Table 5.

Supportive care, treatment of Bing–Neel syndrome (BNS) and transformed WM, and the role of autologous and allogeneic transplants are covered in Box 3.

Conclusion

Improved understanding of WM biology, including recognition of MYD88 L265P, has led to the development of

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BOX 3 Additional treatment

1 Supportive care

Plasmapheresis:

- Symptomatic hyperviscosity and asymptomatic patients with IgM levels >60 g/L at diagnosis or during treatment should be managed urgently with plasmapheresis, especially in patients with concomitant cryoglobulinaemia.
- Avoidance of red cell transfusions is recommended in this setting; if necessary, this should be timed to follow plasmapheresis.
- Careful fluid management to prevent exacerbation of hyperviscosity and acute pulmonary oedema is required.

Iron replacement:

- Iron infusions may be useful for the management of functional iron deficiency secondary to hepcidin excess. Patients not demonstrating a rise in hemoglobin levels within weeks of starting a BTKi should be screened and treated for iron deficiency. Target ferritin >200 μg/L and transferrin saturation >20% is recommended.

Neuropathy:

- The sensorimotor neuropathy of WM can be partially reversed with rituximab-based therapy in some patients. Management of neuropathy should be undertaken in conjunction with a neurologist.

Nephropathy:

The presence of nephropathy often requires careful diuresis and fluid management because of extravascular fluid, in consultation with a renal physician. Appropriate investigations, including renal biopsy and treatment of the underlying Waldenström clone, should be considered as part of multidisciplinary discussions.

Infections:

- Despite the lack of specific data in patients with WM, antimicrobial, antiviral and antifungal prophylaxis is recommended for those who develop recurrent or life-threatening infections, especially while on therapy.
- The use of intravenous or subcutaneous immunoglobulin therapy should be considered in patients with hypogammaglobulinaemia and serious or recurrent infections.
- Management of COVID-19 in patients with WM should be consistent with current guidelines and regulations.[15,16]

2 Stem cell transplantation

- Frontline allogeneic stem cell transplantation (ASCT) in WM (reported a median PFS of 60 months) is not sufficiently superior to DRC or BTKi to justify the cost and toxicity (Table 6). ASCT is therefore not recommended in the frontline setting.
- Retrospective studies have reported a median PFS of 3 to 4 years in relapsed patients. There are no data on the role of ASCT in the BTKi era; however, ASCT would be a reasonable option in patients with aggressive disease and/or intolerance to BTKis.
- ASCT is used rarely and is reserved for younger, fit patients with aggressive R/R disease or transformed WM, who have a suitable donor and/or are resistant/intolerant to BTKis.

3 Bing–Neel syndrome

- BNS is a rare neurologic complication of WM, caused by malignant lymphoma cells infiltrating the central nervous system, resulting in a range of neurologic sequelae such as headaches, cognitive deficits, paresis and psychiatric manifestations.[17]
- The clinicopathologic entity can occur after or before a definitive diagnosis of WM (characterised by BM infiltration and IgM paraproteinaemia).
- Diagnostic criteria developed by the 8th IWWM include the demonstration of monoclonal lymphoid cells with the characteristic phenotype (using flow cytometry, immunohistochemistry and/or monoclonal IgH) in cerebrospinal fluid (CSF) or on histological biopsy.
- Other investigations include testing for MYD88 L265P mutation on CSF and imaging of the brain and spinal cord using CT and/or magnetic resonance imaging.
- A recent international retrospective study on single-agent ibrutinib in 28 patients with BNS showed symptomatic and radiologic improvements in 85% and 60% of patients, respectively, within 3 months of treatment. The 2-year event-free survival rate with ibrutinib was 80%, the 2-year ibrutinib survival rate was 81% and the 5-year BNS survival rate was 86%.[18] Based on this study, the use of BTKis is recommended for BNS.

4 Transformation to large cell disease

- Histological transformation to diffuse large B-cell lymphoma (DLBCL) can be confirmed on tissue biopsy. PET scan may be particularly useful in the diagnosis of large cell transformation.
- DLBCL occurring in the context of antecedent WM is known to occur from clonal evolution of the underlying WM or as an independent clone.[19]
- Most cases of transformation involve extranodal sites, commonly CNS, cutaneous or testicular.
- Patients with transformed WM can be treated with intensive chemotherapy regimens used for de novo DLBCL. Responsive and fit patients may be considered for autologous and/or allogeneic transplantation.

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Table 5 Overview of published regimens for the treatment of WM

Regimen (*N*)	*N*	Overall response (%)	Median PFS	AML/MDS	Median OS	Comments
Frontline studies						
Bendamustine + rituximab	22	95%	70 months	<1%	–	
Bendamustine + rituximab	116	86%	–	–	–	
Rituximab, cyclophosphamide, dexamethasone	72	74% (CR 7%)	35 months	1%	95 months	
Ibrutinib	99	77% (19% VGPR)	84% PFS at 18 months	N/A		Patients with mutated only
Rituximab + ibrutinib versus placebo	150	72% versus 32% major response rate ($P < 0.001$)	At 30 months, PFS 82% versus 28% (HR, 0.20; $P < 0.001$)	N/A		Independent of MYD88 genotype
Zanubrutinib	101	78% major response rate (28% VGPR)	85% PFS at 18 months	N/A		Effective independent of MYD88 genotype
IDR	28	96%	40 months			
Chlorambucil (Mayo)	46	64–75%	26–46 months	9%	5.4 years	
Chlorambucil (WM1)	209	39%	27 months	3%	69.8 months	
Fludarabine (WM1)	209	48%	36 months	0.5%	NR	
Fludarabine (SWOG)	118	38% (CR 3%)	60 months	NR	5-year OS 62%	
Cladribine	26	85% (CR 12%)	NR	NR	–	
Fludarabine + rituximab	27	89% (CR 4%)	77 months	4%	–	
Cladribine + rituximab	16	94%	65+ months	0%	–	
FC + rituximab	28	93% (CR 15%)	51+ months	0%	–	
R-CHOP (GLSG)	23	91% (CR 9%)	63 months	NR	–	
R-CHOP (StiL 1–2003)	19	95%	28 months	<1%	–	
Bortezomib (NCIC)	27	25%	16 months	NR	–	
Bortezomib + rituximab	26	65% (CR 4%)	12+ months	NR	–	0% PN
Bortezomib + dexamethasone + rituximab	23	83% (CR 13%)	30+ months	NR	–	30% PN
Bortezomib + dexamethasone + rituximab	59	68% (CR 3%)	42 months	NR	3-year OS 81%	7% PN
Carfilzomib + dexamethasone + rituximab	31	68% (CR 3%)	55% at 2 years	NR	–	
Relapsed/refractory studies						
Bendamustine + various	30	83% (CR 0%)	13 months	3%	–	
Bendamustine + rituximab	13	NR	32 months	NR	–	
Ibrutinib	63	90.5%	2-year PFS 69%; 5-year PFS NR	N/A	5-year OS 87%	5-year PFS 70% versus 38% for MYD88 (mutated) CXCR4 (wild-type) and MYD88 (mutated) CXCR4 (mutated) ($P = 0.02$)
Zanubrutinib	101	78% (VGPR 28%)	85% PFS at 18 months	N/A		Effective independent of MYD88 genotype
Venetoclax	32	84%	30 months			
IDR	59	71% (VGPR 14%)	NR			
Cyclophosphamide, adriamycin, prednisolone	45	11%	3 months	4%	41 months	
Fludarabine (phase III)	45	30%	19 months	9%	45 months	
Fludarabine (SWOG)	64	33% (CR 0%)	30% at 5 years	NR	5-year OS 50%	
Cladribine	46	43%	12 months	NR	–	
Fludarabine + rituximab	20	81% (CR 5%)	38 months	10%	–	
Fludarabine + various	19	74%	36 months	16%	–	
FC + rituximab	40	80% (CR 10%)	77 months	5%	–	

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Table 5 *Continued*

Regimen (*N*)	*N*	Overall response (%)	Median PFS	AML/MDS	Median OS	Comments
Cladribine + rituximab	13	85%	>65 months	0%	–	
Bortezomib (Greek)	10	60% (CR 0%)	NR	NR	–	20% G3 PN
Bortezomib (WMCTG)	27	48% (CR 0%)	7 months	NR	–	22% G3 PN
Bortezomib (NCIC)	15	27% (CR 0%)	16 months	NR	–	19% G3 PN
Bortezomib + rituximab	37	52%	17 months	NR	–	
Bortezomib + rituximab	10	90%	NR	NR	–	
Ibrutinib[9]	63	73% (CR 0%)	24+ months	NR	2-year OS 95%	
Autologous stem cell transplantation						
Consolidation of first response	12	100% (CR 17%)	69 months	NR	NR	Subset population
Consolidation of first response	69	NR	60 months	NR	–	
All disease stages	10	NR	36+ months	NR	3-year OS 70%	NRM 11%
All disease stages	158	NR	48 months	4%	5-year OS 68.5%	NRM 5.6%
Allogeneic stem cell transplantation (ASCT)						
ASCT MAC RIC	MAC: 37 RIC: 49	ORR, 75.6%	MAC: 56% at 3 years RIC: 49% at 3 years		MAC: 62% at 3 years RIC: 64% at 3 years	MAC: 33% at 3 years RIC: 23% at 3 years

AML, acute myeloid leukemia; FC, fludarabine + cyclophosphamide; GLSG, German Low Grade Lymphoma Study Group; IDR, ixazomib + dexamethasone + rituximab; MDS, myelodysplastic syndrome; N/A, not available; NCIC, National Cancer Institute of Canada Clinical Trials Group; NRM, nonrelapse mortality; PN, peripheral neuropathy; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; StiL, Study Group of Indolent Lymphomas; WM1, Trial Comparing Chlorambucil to Fludarabine in Patients With Advanced Waldenström Macroglobulinemia; WMCTG, Waldenström's Macroglobulinemia Clinical Trials Group.

Table 6 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 nonrandomised 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 nonexperimental 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 a randomised controlled trial of good quality addressing specific recommendation (evidence levels 1A and 1B)
B	Recommendation based on well-conducted studies but no randomised controlled trial on the topic of recommendation (evidence levels 2A, 2B and 3)
C	Recommendation based on expert opinions or reports (evidence level 4)

targeted therapies such as the BTKi. Unique aspects of WM management, such as IgM flare on cessation of BsTKi, pose challenges to less experienced clinicians and underscore the need for disease-specific treatment guidelines. Given the rapid advances in WM therapy, enrolment of patients into WM-specific clinical trials is strongly encouraged.

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References

1 Swerdlow SHCE, Harris NL, Jaffe ES, Plieri SA, Stein H, Thiele J. *WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues*, 4th edn. Lyon: IARC; 2017.
2 Talaulikar D, Tam CS, Joshua D, Ho JP, Szer J, Quach H *et al*. Treatment of patients with Waldenstrom macroglobulinaemia: clinical practice guidelines from the Myeloma Foundation of Australia Medical and Scientific Advisory Group. *Intern Med J* 2017; **47**: 35–49.
3 Talaulikar D, Joshua D, Ho PJ, Gibson J, Quach H, Group, A, et al. Consensus clinical practice guidelines for the treatment of patients with Waldenström Macroglobulinaemia; 7 June 2022. Available from URL: https://myeloma.org.au/wp-content/uploads/2022/06/MSAG_waldenstro%CC%88m-guidelines_jun22.pdf
4 Maqbool MG, Tam CS, Morison IM, Simpson D, Mollee P, Schneider H *et al*. A practical guide to laboratory

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investigations at diagnosis and follow up in Waldenstrom macroglobulinaemia: recommendations from the Medical and Scientific Advisory Group, Myeloma Australia, the Pathology Sub-committee of the Lymphoma and Related Diseases Registry and the Australasian Association of Clinical Biochemists Monoclonal Gammopathy Working Group. *Pathology* 2020; **52**: 167–78.
5 Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C *et al*. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet* 2013; **381**: 1203–10.
6 Rummel MJ, Lerchenmüller C, Greil R, Goerner M, Hensel M, Engel E, et al. Bendamustin-rituximab induction followed by observation or rituximab maintenance for newly diagnosed patients with Waldenström's macroglobulinemia: results from a prospective, randomized, multicenter study (StiL NHL 7–2008 –MAINTAIN-; ClinicalTrials.gov Identifier: NCT00877214). ASH abstract 2012 (abstract).
7 Rummel M, Kaiser U, Balser C, Stauch M, Brugger W, Welslau M *et al*. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. *Lancet Oncol* 2016; **17**: 57–66.
8 Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Zervas K, Tsatalas C, Kokkinis G *et al*. Primary treatment of Waldenstrom macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol* 2007; **25**: 3344–9.
9 Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R *et al*. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med* 2015; **372**: 1430–40 (In eng).
10 Dimopoulos MA, Tedeschi A, Trotman J, García-Sanz R, Macdonald D, Leblond V *et al*. Phase 3 trial of ibrutinib plus rituximab in Waldenstrom's macroglobulinemia. *N Engl J Med* 2018; **378**: 2399–410.
11 Dimopoulos MA, Trotman J, Tedeschi A, Matous JV, Macdonald D, Tam C *et al*. Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol* 2017; **18**: 241–50.
12 Trotman J, Opat S, Gottlieb D, Simpson D, Marlton P, Cull G *et al*. Zanubrutinib for the treatment of patients with Waldenstrom macroglobulinemia: 3 years of follow-up. *Blood* 2020; **136**: 2027–37.
13 Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G *et al*. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. *Blood* 2020; **136**: 2038–50.
14 Dimopoulos M, Sanz RG, Lee HP, Trneny M, Varettoni M, Opat S *et al*. Zanubrutinib for the treatment of MYD88 wild-type Waldenstrom macroglobulinemia: a substudy of the phase 3 ASPEN trial. *Blood Adv* 2020; **4**: 6009–18.
15 Talaulikar D, Advani RH, Branagan AR, Buske C, Dimopoulos MA, D'Sa S *et al*. Consensus statement on the management of Waldenstrom macroglobulinemia patients during the COVID-19 pandemic. *Hemasphere* 2020; **4**: e433.
16 Buske C, Dreyling M, Alvarez-Larran A, Apperley J, Arcaini L, Besson C *et al*. Managing hematological cancer patients during the COVID-19 pandemic: an ESMO-EHA Interdisciplinary Expert Consensus. *ESMO Open* 2022; **7**: 100403.
17 Minnema MC, Kimby E, D'Sa S, Fornecker LM, Poulain S, Snijders TJ *et al*. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. *Haematologica* 2017; **102**: 43–51.
18 Castillo JJ, Itchaki G, Paludo J, Varettoni M, Buske C, Eyre TA *et al*. Ibrutinib for the treatment of Bing-Neel syndrome: a multicenter study. *Blood* 2019; **133**: 299–305.
19 Talaulikar D, Biscoe A, Lim JH, Gibson J, Arthur C, Mackinlay N *et al*. Genetic analysis of Diffuse Large B-cell Lymphoma occurring in cases with antecedent Waldenstrom Macroglobulinaemia reveals different patterns of clonal evolution. *Br J Haematol* 2019; **185**: 767–70.
20 Kyle RA, Benson JT, Larson DR, Therneau TM, Dispenzieri A, Kumar S *et al*. Progression in smoldering Waldenstrom macroglobulinemia: long-term results. *Blood* 2012; **119**: 4462–6.
21 Castillo JJ, Advani RH, Branagan AR, Buske C, Dimopoulos MA, D'Sa S *et al*. Consensus treatment recommendations from the tenth International Workshop for Waldenstrom Macroglobulinaemia. *Lancet Haematol* 2020; **7**: e827–37.
22 Anderson KC, Alsina M, Bensinger W, Biermann JS, Cohen AD, Devine S *et al*. Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma, version 2.2013. *J Natl Compr Canc Netw* 2012; **10**: 1211–9 (In eng).

Appendix I

International Consensus Statements on Treatment of WM

Two main international consensus statements on the therapy of WM exist, one from the IWWM,[21] the second from the National Comprehensive Cancer Network (NCCN).[22] The IWWM guidelines were published before the data on zanubrutinib were published.

The IWWM guidelines emphasise the following principles:

1 Recommended first-line regimens were: (a) BTKi, (b) B-R (bendamustine and rituximab), (c) DRC (dexamethasone, rituximab and cyclophosphamide) or (d) bortezomib, rituximab and dexamethasone.
2 Rituximab maintenance is not recommended because of the current paucity of evidence.

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3 R-CHOP and fludarabine-based regimens were specifically recommended against in the frontline.
4 In BTKi-naïve patients, BTKi therapy is recommended at relapse.
5 Salvage therapy after remissions of ≥12 months may include repeat administration of the induction chemo-immunotherapy regimen, especially if a BTKi is contraindicated.
6 Salvage options after shorter remissions include recruitment to clinical trials, BTKi therapy, switching to different chemotherapy, bortezomib or an ixazomib-based regimen (including fludarabine combinations) and in the appropriate clinical context, ASCT.

The major difference between the IWWM guidelines and Australian practice is the lack of public funding for bortezomib and BTKi except for zanubrutinib, for the treatment of WM in Australia, noting that zanubrutinib has been recently been approved by the PBS.

The NCCN guidelines are similar to the IWWM guidelines, with an increased emphasis on bortezomib-based or DRC induction because of the 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 ≥4 cP being associated with hyperviscosity complications. This test is not universally available in Australia, where judgments regarding the severity of hyperviscosity manifestations were commonly made on clinical features.

Appendix II

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