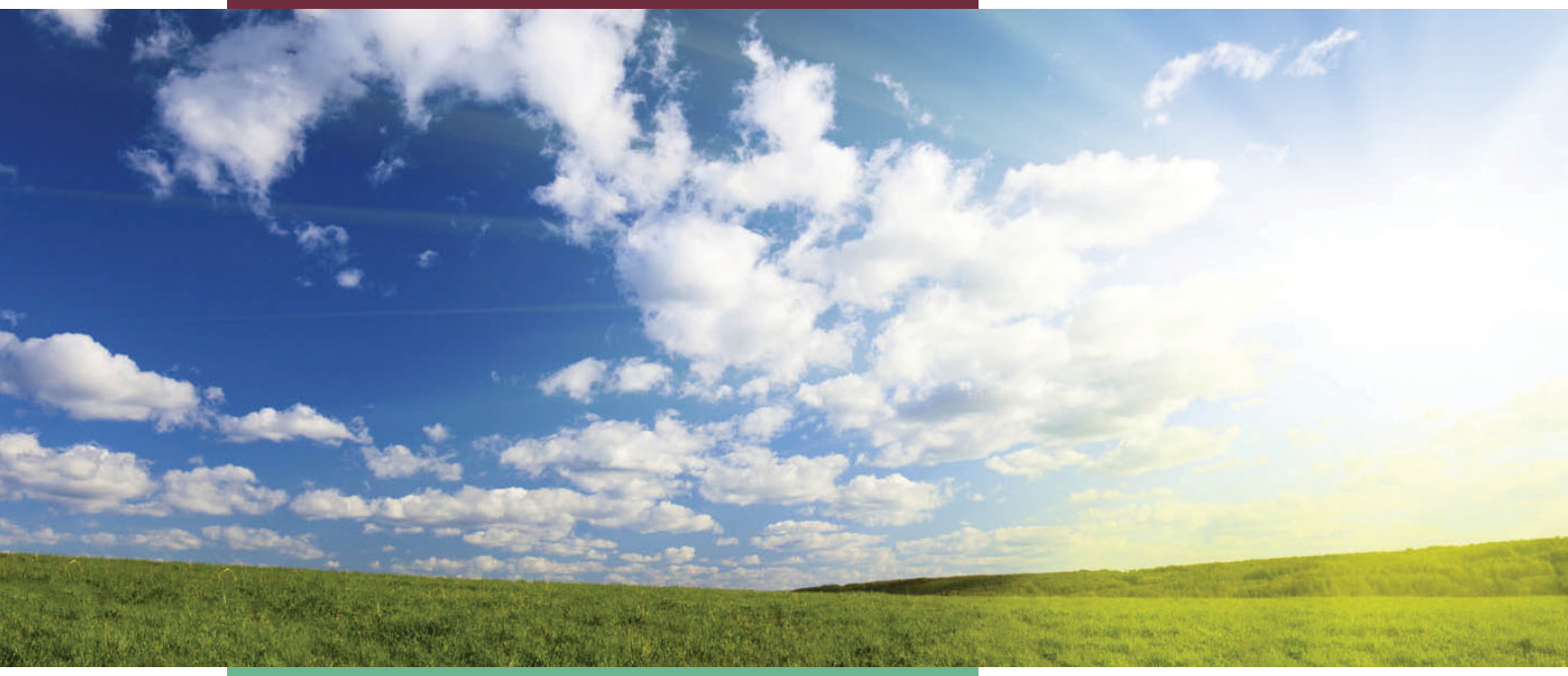
CLINICAL PRACTICE STATEMENT BY THE MEDICAL SCIENTIFIC ADVISORY GROUP TO MYELOMA AUSTRALIA

Myeloma Australia

June 2022



MSAG Guidelines

Consensus clinical practice guidelines for the treatment of patients with Waldenström Macroglobulinaemia

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Acknowledgements:

These guidelines have been reviewed and endorsed by the WMozzies.

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1 INTRODUCTION

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 low dose chemoimmunotherapy. Recent trials have demonstrated the efficacy and safety of Bruton's Tyrosine Kinase inhibitors (BTKi) in WM, both as monotherapy and in combination with other drugs. There is emerging evidence on use of other agents including BCL2 inhibitors and on treatment of rare presentations of WM. In this update, the Medical and Scientific Advisory Group to the Myeloma Foundation Australia review available evidence on treatment of WM since the last publication in 2017 and provide specific recommendations to assist Australian clinicians in the management of this disease.

Introduction

Waldenström Macroglobulinaemia (WM) is a B-cell lymphoid malignancy which 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. It constitutes less than 5% of all non-Hodgkin lymphoma (NHL), with an incidence of ≈0.3/100,000 cases/year 2. The advent of newer treatments such Bruton's tyrosine kinase inhibitors (BTKi) have changed the diagnostic and therapeutic landscape of the disease.

This update to the clinical practice guideline for the treatment of WM is from the Australian Medical Scientific Advisory Group (MSAG) to Myeloma Australia (MA), 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.

It encompasses general comments on approved treatment options, followed by sections on various therapies, and recommended options for newly diagnosed WM and relapsed/refractory WM.

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).

Table 1: Level of evidence and grades of recommendations.

2 TREATMENT OF WM: GENERAL COMMENTS

Patients considered to be candidates for treatment include those with cytopenias i.e. Hb level < 100 g/L or platelet count < 100 x 10^9/L attributable to WM, those with bulky lymphadenopathy or organomegaly, symptomatic hyperviscosity, moderate/severe or worsening peripheral neuropathy attributable to WM, amyloidosis, cryoglobulinemia, nephropathy or cold-agglutinin disease (**Table 2**).

Feature	IgM-Monoclonal Gammopathy of Undetermined Significance (MGUS)	Asymptomatic Waldenström Macroglobulinaemia (WM)96	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 5 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 109/L Platelet <100 x 109/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.

Table 2: The Spectrum of IgM Gammopathy, and Treatment Indications [3]

The general recommended work up of patients with WM has been covered in detail in a previously published MSAG guideline [4] and is listed in **Table 3**. Asymptomatic patients should have IgM levels monitored serially and those with rapidly rising levels or with IgM > 60 g/L should be considered for treatment to avoid hyperviscosity related complications [5] . Two thirds of patients with IgM > 60 g/L are known to develop hyperviscosity. Hyperviscosity rates are reported to be higher in those carrying CXCR4 mutations [6].

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 [97] 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.
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

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

Table 3: Recommended Workup for WM[3]

Approved treatment regimens for therapy in Australia

Australian clinicians are limited in the access to Pharmaceutical Benefits Scheme (PBS) subsidised drugs for treatment of WM. The standard chemoimmunotherapy regimens approved for use in WM through the PBS are Bendamustine-Rituximab (B-R) and Dexamethasone-Rituximab-Cyclophosphamide (DRC). B-R is publicly funded only for frontline treatment. As this is an update to the previous guidelines, conventional chemoimmunotherapy regimens outside of these 2 regimens that were discussed in version 1 of the MSAG clinical practice recommendations for WM will not be discussed again. Please refer to them for further details [3].

Newer agents such as BTKi, while effective, are not yet reimbursed through the PBS in Australia at the time of publication of these guidelines. Treatment recommendations for WM based on availability of drugs through PBS has therefore not changed from the time of version 1 of the guidelines published in 2017. It is however recommended that for appropriate clinical contexts, alternate means of procuring medications be explored, noting that Zanubrutinib has recently received positive recommendation from the PBAC to be listed on the PBS.

Before discussing newer specific therapeutic regimens in WM, it is important to highlight additional management aspects unique to WM.

1. IgM flare or rebound

While IgM levels are traditionally believed to correlate with disease status, this is not always the case. A phenomenon that rapidly causes > 25% rise in IgM levels called “IgM flare” or “IgM rebound” is seen after commencing Rituximab based therapy, especially Rituximab monotherapy, and after cessation or interruption of BTKi.

Approximately 54% of patients receiving Rituximab are known to develop IgM flare; they tend to show this in the first 8 weeks of treatment, with levels returning to baseline within 4 months in most patients [7 8].

A similar phenomenon is noted on cessation or interruption of the first generation BTKi, Ibrutinib in 73% of patients with approximately half of these rebounds occurring within the first 4 weeks. About half i.e. 46% return back to pre-Ibrutinib levels. However, the important point to note is that the IgM rebound can persist for much longer i.e. 6 months following re-initiation of therapy, and persistent elevation of IgM after recommencement of Ibrutinib does not necessarily represent treatment failure [9]. If in doubt, continued BTKi therapy with regular monitoring of symptoms and IgM levels is recommended. Rarely, hyperviscosity symptoms including cerebral symptoms and worsening neuropathy can occur, and temporary treatment with plasmapheresis may be warranted.

2. Monitoring pre and post treatment and response assessment

WM patients require monitoring during the asymptomatic phase, and post treatment for response assessment. There are particular inherent difficulties in IgM / paraprotein measurements irrespective of whether monoclonal paraprotein determined by serum electrophoresis and densitometry is used for monitoring, or total IgM as measured by nephelometry. We recommend that serial measurement be performed, preferably at the same laboratory, as the unique IgM monoclonal protein can be difficult to measure in individual patients due to technical factors [10,11]. 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.

It should be noted that there is lack of correlation between disease burden as assessed by bone marrow (BM) and CT evaluations, IgM levels and the clinical situation. For example, disease progression manifested by development of symptoms and/or anaemia, may present with significant BM infiltration with malignant cells but relatively small rise in IgM levels. Clinical judgement is required to carefully assess the patient comprehensively instead of relying on IgM levels alone.

The International Workshop on Waldenström Macroglobulinaemia (IWWM) has published response categories based mainly on IgM responses [12]: 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 4**).

It is important to know that post therapy drop/nadir in IgM levels may be delayed for months to years in some clinical responders. Perversely, the uncommon occurrence of delayed paraprotein responses can occur months to years after cessation of time limited chemoimmunotherapy [13,14]. Therefore, 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 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.

	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		

Table 4: International Workshop on Waldenström Macroglobulinaemia (IWMM) response criteria

3 TREATMENT OPTIONS

Chemoimmunotherapy

Within the current Australian regulatory environment, the most pragmatic regimens for frontline therapy, 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). There is no randomised data on comparison of the 2 regimens. BR and DRC are discussed in greater detail below. Doses and schedules of B-R, DRC, FCR, FR, and single agent chlorambucil and rituximab are listed in **Table 5**.

Bendamustine-Rituximab (B-R)

The large, randomised StiL study comparing Bendamustine and Rituximab with R-CHOP in 549 indolent and mantle cell lymphomas in the frontline setting included 41 patients (22: B-R arm, 19: R-CHOP arm) with lymphoplasmacytic lymphoma/Waldenström 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)[15]. Preliminary analysis on the B-R induction arm of the randomised controlled trial on Rituximab maintenance vs. observation in treatment naïve WM showed an overall response rate (ORR) of 86% [16]. This study is the basis on which anthracycline-based therapy such as R-CHOP is no longer recommended in WM. As Bendamustine and Rituximab are both now PBS-funded, B-R is a preferred first line therapy for WM.

The StiL MAINTAIN study randomised 218 WM patients who had at least partial response to B-R to observation vs 2 monthly Rituximab maintenance for 2 years. The median PFS of 83 vs 101 months was not significant [17]. There is therefore currently no data to recommend use of Rituximab maintenance in WM.

B-R has also been studied in the relapsed setting with median reported PFS of 13.2 months [18]. 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 F-R i.e. Fludarabine and Rituximab (34.2 months vs. 11.7 months, HR = 0.54, p<0.0001) [19]. 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.

DRC (Dexamethasone, Rituximab and Cyclophosphamide)

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) [20,21] (**Table 6**). 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. It may be the preferred regimen for the frailer, older patient for whom Bendamustine may be considered too immunosuppressive, especially in those elderly with indolent disease and very slow progression to need for therapy who may not require the more intensive and immunosuppressive bendamustine approach in their lifespan.

Other chemo(immunotherapy) regimens

There is considerable data on use of nucleoside analogues such as Fludarabine and Cladribine based regimens in the frontline treatment of transplant ineligible WM. The randomised WM1 study [22] and the phase 2 SWOG study [23] included 209 and 118 WM patients respectively and showed ORR of 28% and 38% with median PFS of 36 and up to 60 months. The addition of Rituximab to fludarabine, fludarabine and cyclophosphamide or to cladribine has been reported to be even higher in phase 2 studies with ORR of 38-85% and PFS of up to 60 months [24-26]. However, nucleoside analogue based regimens are no longer recommended because of the risk of bone marrow and stem cell toxicity [27] and the risk of secondary myeloid neoplasms and disease transformation [28 29].

Similarly, single agent Chlorambucil is no longer recommended because of poorer PFS of 26-46 months and higher risk of secondary myeloid neoplasms of 3-9% [22,30].

Single agent Rituximab is not advised because of poor overall response rates of 52%, short median time to progression of 16 months for treated and untreated patients, and risk of IgM flare in >50% [7,8,31]. A recent phase 2 study on single agent Ofatumumab found similar overall response rate of 51% but with a lower rate of IgM flare of 9% [32].

The only significant randomised controlled study in the setting of relapsed WM is the French CAP (cyclophosphamide, adriamycin and prednisolone) vs. fludarabine study [33]. In this study, patients salvaged with CAP had poor ORR and a short median PFS of only 3 months, again 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 [5,18,34-37] (**Table 6**).

Proteasome inhibitors:

Several studies using proteasome inhibitor based regimens including Bortezomib and Carfilzomib have been conducted in WM [38-43]. In general, combinations of proteasome inhibitors and rituximab achieve an overall response rate (ORR) of 65–83% and median PFS of 2–4 years, somewhat inferior to those seen with fludarabine- or Bendamustine-based regimens. Their advantages include a rapid paraprotein response, hypothesised to be due to plasma cell depleting effect [44], which may be particularly beneficial in patients with hyperviscosity syndrome, high IgM levels, renal disease and amyloidosis. They also carry the benefit of lack of stem cell toxicity and reduced risk of MDS. Furthermore, bortezomib has been reported to be particularly beneficial in patients with familial disease [45]. However, bortezomib can exacerbate WM-related neuropathy, with reported grade 3–4 neuropathy rates of 20–30% when given twice weekly and intravenously [38,40-42]. This risk may be reduced by administering bortezomib weekly [40,46] or by the use of the second-generation proteasome inhibitor carfilzomib which does not commonly cause neuropathy [43]. 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.

Carfilzomib is known to increase the risk of cardiovascular events in multiple myeloma. This should also be taken into consideration in older patients with WM with history of cardiovascular disease[47].

Regimen	Dose and Schedule	Comment
B-R [15]	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
DRC [20]	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
Ibrutinib [63]	420 mg OD	Limited to MYD88 mutated cases.
Ibrutinib + Rituximab [58]	420 mg OD Rituximab 375 mg/2	Independent of MYD88 genotype
Zanubrutinib [63]	160 mg BD or 320 mg OD PO	
IDR [49]	Ixazomib PO 4 mg and Dexamethasone PO/IV 20 mg Days 1, 8, 15 Rituximab 375 mg/m2 Day 1 every 28 days	
FR [24,98]	*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 [26,98]	*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 [98]	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 [99]	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”.

Table 5: Doses and Schedules of Frontline Regimens for WM

In the United States, these proteasome-based regimens are commonly used in the salvage setting, producing median remission durations of approximately 12 - 18 months [38,39,41,42,48].

Ixazomib is an oral proteasome inhibitor which has been trialled with good results in both treatment naïve and relapsed WM. A prospective phase II study of oral ixazomib with dexamethasone and rituximab in 26 symptomatic treatment naïve patients found ORR of 96% with major responses in 77% at a median follow up of 22 months [49]. Long term follow up further showed median PFS and time to next treatment (TTNT) of 40 months each, duration of response of 38 months and VGPR of 19%. The treatment regimen was well tolerated without significant neurological or cardiac toxicity [50]. A similar regimen combining Ixazomib with oral dexamethasone and subcutaneous administration of Rituximab in a multicentre phase I/II study in 56 relapsed refractory WM patients (median number of previous treatments =2, range 1-7), showed ORR of 71% and PFS of 56% at median follow up of 24 months [51]. This regimen shows promise as an alternative to current chemoimmunotherapy regimen.

BTKi

BTK is a non-receptor tyrosine kinase, with a central role in B-cell signalling in normal B-cell development. It plays a role in the molecular cascade downstream of the B-cell receptor (BCR) resulting in activation of the phosphoinositide-3-kinase (P13K)–protein kinase B (AKT) pathway, phospho- lipase C (PLC), protein kinase C (PKC), and nuclear factor κB(NF-κB) with consequent B-cell differentiation, proliferation, and survival [52,53].[30–32] BTK also has a role in the signalling of G-coupled chemokine receptors (like CXCR4), cytokine receptors (CD19, CD38 CD40), tumor necrosis family receptors (TNFRs), integrins and toll-like receptors (TLRs), such as TLR/MYD88 [54].

The BTK signalling pathway is constitutively activated in WM, causing survival of malignant B cells, and making it an ideal target for therapeutic inhibition. Activating mutations of MYD88, seen in > 90% of WM, are associated with increased down- stream BTK signalling, providing further therapeutic rationale for BTK inhibition [55].

BTKis covered in this guideline are the first-generation inhibitor, Ibrutinib, and the second-generation inhibitors Zanubrutinib, Acalabrutinib and Tirabrutinib, with particular focus on Ibrutinib and Zanubrutinib.

Ibrutinib

Ibrutinib is a first-in-class oral BTKi, which binds irreversibly and covalently with a cysteine residue on site 481 of the binding site of BTK, with several downstream effective mechanisms. These include activation of apoptosis, inhibition of DNA replication, blocking of pro-survival signalling pathways via inhibition of HCK and NFkB, and immunomodulatory effects on the tumour microenvironment.

In 2015, the United States Food and Drug Administration (FDA) licensed Ibrutinib for the treatment of relapsed WM, based on a landmark phase II study[56]. In this study, ibrutinib at a dose of 420 mg daily, achieved an ORR of 73% (with no CRs) in 63 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% [56]. The long-term follow up of this cohort showed ORR and major response rates of 91% and 79% at median follow up of 59 months [57]. Patients with mutated MYD88 and wildtype (WT) CXCR4 showed higher response rates and shorter times to response. Median PFS was 0.4 years in patients with MYD88 WT cases, and 5-year PFS was 70% vs 38% for CXCR4 WT vs CXCR4 mutated cases indicating poor efficacy in patients who are MYD88 WT, and those who are MYD88 mutated but carry CXCR4 mutations (noting the limitations of small sample size in drawing these conclusions) [57].

The INNOVATE phase 3 randomised trial of Rituximab with Ibrutinib vs rituximab monotherapy included 150 symptomatic patients who were treatment naïve or relapsed/refractory to previous treatments. The PFS at 30 months was 82% and was independent of MYD88 or CXCR4 genotype. Hypertension and atrial fibrillation were noted at rates of 13% and 12% respectively, and infusion-related reactions of 16%[58].

A third arm of the study enrolled 31 Rituximab refractory patients (median number of prior treatments =4) and treated them with Ibrutinib monotherapy, achieving ORR of 90% and 18 month PFS of 86% [59]. This study did not directly compare Ibrutinib monotherapy vs Ibrutinib with Rituximab. As there is no direct head-to-head comparison of ibrutinib vs ibrutinib-rituximab in current clinical trials, both ibrutinib monotherapy and ibrutinib-rituximab are approved for the treatment of WM in the USA.

Zanubrutinib

Zanubrutinib is an oral second generation BTKi which binds irreversibly to the Cys481 residue of the adenosine triphosphate (ATP)-binding pocket of the BTK active site. It has high selectivity for BTK, equal potency to first generation inhibitors, and less off-target effect on epidermal growth factor receptor (EGFR), interleukin-2-inducible T-cell kinase (ITK), Janus tyrosine kinase 3 (JAK3), human epidermal growth factor receptor 2 (HER2), and TEC-family kinases [60]. The first-in-human studies with this drug in chronic lymphocytic leukaemia (CLL) demonstrated potent antitumor activity, was well tolerated, and demonstrated an overall response rate of 96.2% [61].

In the phase I/II study BGB-3111 AU-003, 77 patients with WM (24 TN and 53 R/R) were also included; they had no prior BTK inhibitor exposure and were treated with Zanubrutinib 160 mg BD or 320 mg OD. Long term data at a median follow-up of 36.0 months for patients with R/R disease and 23.5 months for TN patients showed ORR of 95.9%, and VGPR/CR rate of 45.2%. The ≥ VGPR rate increased over time - it was 20.5% at 6 months, 32.9% at 12 months, and 43.8% at 24 months. The estimated 3-year progression-free survival rate was 80.5%, and overall survival rate was 84.8% [62].

At median follow up, almost three quarters of patients remained on treatment. Reasons for treatment discontinuation included any adverse events in 13.0% of patients, disease progression (10.4%), and other causes (3.9%) [62].

The landmark phase 3 ASPEN study compared Ibrutinib monotherapy (n=99) with 160 mg BD of Zanubrutinib (n=101) in 201 symptomatic WM patients who had the MYD88 mutation [63]. Results showed similar PFS at 18 months of 84 and 85%, major response rate (MRR), and a non-statistically significant difference in VGPR of 19% vs 28% favouring zanubrutinib (p=0.09). There were no CRs. Adverse events including cardiovascular toxicity (especially AF and grade 3+ hypertension) and those resulting in discontinuation of treatment were less often seen with Zanubrutinib. While neutropenia was more common with Zanubrutinib, ≥ grade 3 infections were similar at 1.2 and 1.1 per 100-person months [63].

In the context of Ibrutinib monotherapy having shown poor outcomes in MYD88 WT WM, the ASPEN study included a cohort of MYD88 neg/unknown patients. Of the 28 patients included in the study (26 MYD88 WT, 2 mutation unknown), 50% achieved a major response and 27% a VGPR. At 18 months, PFS and OS were 68% and 88% respectively. This important sub-study established the efficacy of Zanubrutinib monotherapy in MYD88 WT patients.

A phase 2 study of 44 Chinese patients with R/R WM with at least 1 prior therapy, treated with Zanubrutinib showed MRR in ~ 70% and VGPR in 32.6%. MYD88 WT cases showed MRR of 50%. Grade 3 neutropenia, thrombocytopenia and pneumonia were seen in 31.8% and 20.5 % each respectively, and there were no cases reported with AF [64].

Although the preferred dose of zanubrutinib is 160mg BD (based on more complete inhibition of BTK over time), available clinical data support activity at both 160mg BD and 320mg daily, with no difference observed to date [65]. The once vs. twice daily dosing schedule can be based on patient preference.

Acalabrutinib

Acalabrutinib (ACP-196), is another oral, second-generation, highly selective, potent covalent BTK inhibitor [66]. Acalabrutinib monotherapy at a dose of 100 mg BD was reported in 106 WM patients, of which 14 were treatment-naïve and 92 were relapsed/refractory patients. The overall response rate was 93% for both TN and for R/R patients at a median follow up of 27.4 months [67]. Of 50 patients with reported genomic studies, the overall response rate was 94% among $MYD88^{L265P}$ mutated patients and 79% among $MYD88^{WT}$ patients. Overall, the responses were similar to those reported with ibrutinib, with a possible superior benefit for the patients with $MYD88^{WT}$. Of the 14 treatment naive patients, 7 patients discontinued treatment (50%); 23 (25%) of 92 relapsed or refractory patients discontinued treatment on study. Grade 3 or higher adverse events reported in more than 5% of patients included neutropenia (16%), and pneumonia (7%). Grade 3-4 atrial fibrillation occurred in one (1%) patient and grade 3-4 bleeding occurred in three (3%) patients. Treatment-related pneumonia and lower respiratory tract infection were reported in 5% and 4% respectively. There were 5 grade 5 events: pneumonia, glioblastoma multiforme, oesophageal carcinoma, myocardial ischemia, and intracranial hematoma but only 1 was considered treatment-related [67].

Tirabrutinib

Tirabrutinib (GS-4059/ONO) is an irreversible, selective BTK inhibitor [68]. In a phase II trial of 27 patients (18 TN, 9 RR), of which 96% carried the MYD88 mutation, the drug resulted in an overall response rate of 94% and 100% among treatment-naïve and previously treated patients with WM after a median follow up of 6.5 and 8.3 months respectively. The median time to major response was 1.87 months. The toxicity profile was manageable, with the most common adverse effects reported to be rash (44%), neutropenia (25.9%), and leukopenia (22.2%). Grade ≥ 3 AEs included neutropenia (11.1%), lymphopenia (11.1%), and leukopenia (7.4%). No grade 5 AEs were noted. All bleeding events were grade 1, and there was no AF or HT reported [69].

Non-covalent BTKi

There are 2 non-covalent reversible BTKi that are being tried in WM - LOXO-305 and ARQ531. This group of drugs has the advantage of non-reliance on covalent binding at C481 site of BTK [70], making them able to bypass resistance mediated by mutations of the C481 site [71].

Recommended phase 2 doses of 200 mg daily of LOXO-305 (Pirtabrutinib) [72] and 65 mg QD of ARQ-531 [73] respectively have been found to have acceptable safety profiles and efficacy, and may potentially fulfil an unmet need in patients resistant to first generation BTKi.

Other novel agents

There are several novel agents being trialled in WM patients.

BCL2 expression has been shown to universally upregulated in WM [74]. A Phase I study with single agent venetoclax in relapsed/refractory B-NHL included 4 WM patients, with ORR 100% [75]. A Phase II study of venetoclax in 32 patients with relapsed/refractory WM patients including 16 previously treated with BTKi showed overall, major, and very good partial response rates of 84%, 81%, and 19%, respectively [76]. All patients carried the ***MYD88 L265P*** mutation, and 17 carried ***CXCR4*** mutations. The median time to minor and major responses was 1.9 and 5.1 months, respectively with previous exposure to BTKis associated with a longer time to response (4.5 ***v*** 1.4 months; $P < .001$). The median progression-free survival was 30 months. Treatment was well tolerated with the only recurring grade ≥ 3 treatment-related adverse event being neutropenia (n = 14; 45%), including only 1 episode of febrile neutropenia, and 1 episode of laboratory reported tumour lysis without clinical findings [76].

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 [77]. Lenalidomide is associated with prolonged anaemia in some patients at standard doses [77] but doses of 15mg/day of lenalidomide have been shown to be safe and efficacious [78]. Intention to treat analysis showed overall response rate of 29%, and median time to progression was 16 months (95% CI 5.5-26) at a median follow up of 36 months. The 5-year OS was reported to be 91%. Grade 3 or higher adverse events at 15 mg Lenalidomide dose included 14% anaemia and 43% neutropenia.

Regimen (N)	N	Overall Response (%)	Median Progression Free Survival	AML/ MDS	Median overall survival (OS)	Comments
FRONTLINE STUDIES						
Bendamustine + Rituximab [15] Bendamustine + Rituximab [16]	22 116	95% 86%	70 months	<1% -	- -	
Rituximab, cyclophosph-amide, dexamethasone (DRC)[20]	72	74% (CR 7%)	35 months	1%	95 months	
Ibrutinib [63]	99	77% (19% VGPR)	84% PFS at 18 months	N/A		In MYD88 mutated patients only
Rituximab + Ibrutinib vs placebo [58]	150	72% vs 32% major response rate (P<0.001)	At 30 months, PFS 82% vs. 28% (HR 0.20; P<0.001)	N/A		Independent of MYD88 genotype
Zanubrutinib [63]	101	78% major response rate (28% VGPR)	85% PFS at 18 months	N/A		Effective independent of MYD88 genotype
Ixazomib + Dexamethasone + Rituximab [49,50]	28	96%	40 months			
Chlorambucil [30] (Mayo) Chlorambucil [98] (WM1)	46 209	64 - 75% 39%	26-46 mths 27 months	9% 3%	5.4 years 69.8 months	
Fludarabine [98] (WM1) Fludarabine [23] (SWOG) Cladribine [100]	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 [24] Cladribine + Rituximab [37] FC + Rituximab [26]	27 16 28	89% (CR 4%) 94% 93% (CR 15%)	77 months 65+ months 51+ months	4% 0% 0%	- - -	
R-CHOP (GLSG) [101] R-CHOP [15](StiL 1-2003)	23 19	91% (CR 9%) 95%	63 months 28 months	NR <1%	- -	
Bortezomib (NCIC) [38]	27	25%	16 months	NR	-	
Bortezomib + Rituximab [46] Bortezomib + Dexa + Ritux [40] Bortezomib + Dexa + Ritux [102]	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 [43]	31	68% (CR 3%)	55% at 2 yr	NR	-	
RELAPSED/ REFRACTORY STUDIES						
Bendamustine + various [18] Bendamustine + Rituximab [19]	30 13	83% (CR 0%) NR	13 months 32 months	3% NR	- =	
Ibrutinib [56,57]	63	90.5%	2 year PFS 69%; 5 year PFS not reached	N/A	5 year OS 87%	5 yr PFS 70% vs. 38% for MYD88(Mut) CXCR4(WT) & MYD88(Mut) CXCR4(Mut), (P = .02)
Zanubrutinib [63]	101	78% (28% VGPR)	85% PFS at 18 months	N/A		Effective independent of MYD88 genotype
Venetoclax	32	84%	30 months			
IDR [51]	59	71% (VGPR: 14%)	Not reached			

table continues next page

Regimen (N)	N	Overall Response (%)	Median Progression Free Survival	AML/ MDS	Median overall survival (OS)	Comments
RELAPSED/ REFRACTORY STUDIES						
Cyclophosphamide, adriamycin, prednisolone [33]	45	11%	3 months	4%	41 months	
Fludarabine (Phase 3) [33] Fludarabine (SWOG) [23] Cladribine [100]	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 [24] Fludarabine + Various [35] FC + Rituximab [36] Cladribine + Rituximab [25]	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) [41] Bortezomib (WMCTG) [42] Bortezomib (NCIC) [38]	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 [39] Bortezomib + Rituximab [48]	37 10	52% 90%	17 months NR	NR NR	- -	
Ibrutinib [56]	63	73% (CR 0%)	24+ months	NR	2yr OS 95%	
AUTOLOGOUS STEM CELL TRANSPLANTATION						
Consolidation of 1st response [84] Consolidation of 1st response [85]	12 69	100% (CR17%) NR	69 months 60 months	NR NR	Not reached -	Subset population
All disease stages [103] All disease stages [85]	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 [104] 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

Table 6: Overview of Published Regimens for the Treatment of WM

4 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 chemoimmunotherapy 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.

Where available, BTKi is recommended as frontline therapy especially in those who are not candidates for chemoimmunotherapy because of age or co-morbidities. Ibrutinib monotherapy is not advised in MYD88 WT patients; for such patients, Ibrutinib and Rituximab regimens appear to have better efficacy. Zanubrutinib monotherapy can be used in patients irrespective of MYD88 genotype, negating the need for testing.

Doses and schedules of B-R, DRC, BTKi, FCR, FR, and single agent chlorambucil and rituximab are listed in **Table 5**.

Initial therapy of WM (adapted from Talaulikar et al[3])

- 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).
- *Ibrutinib monotherapy is recommended if available in MYD88 mutated patients (Level 1B, grade A). In MYD88 WT genotype, it is recommended that Ibrutinib be combined with Rituximab (Level 1B, grade A).
- *Zanubrutinib monotherapy is effective irrespective of MYD88 genotype, with fewer off-target effects, and is recommended if available (Level 1B, grade A).
- Fludarabine-based regimens such as FCR or FR 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 on stem cell mobilisation; and may increase the risk of MDS /AML. 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 to fludarabine (Level I, Grade A). It is therefore not recommended for treatment.
- 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 especially as single agent 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).

**Please note at the time of submission of the manuscript, these drugs are not funded by PBS for frontline treatment.*

Treatment of relapsed WM

There is no standard treatment for relapsed WM and the options depend on (1) availability of novel agents, (2) quality and duration of first response, (3) patient fitness and tolerance of therapy, and (4) whether there is unresolved toxicity from previous therapies such as neuropathy or myelosuppression. Published results of relapsed WM therapy are summarized in **Table 6**.

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).
- *Ibrutinib monotherapy is recommended if available in MYD88 mutated patients (Level 1B, grade A). In MYD88 WT genotype, it is recommended that Ibrutinib be combined with Rituximab (Level 1B, grade A).
- *Zanubrutinib monotherapy is effective irrespective of MYD88 genotype, with fewer off-target effects, and is recommended if available (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 submission of the manuscript, these drugs are not funded by PBS for treatment.*

Supportive care

Urgent management of symptomatic hyperviscosity at diagnosis or during treatment may be required using plasmapheresis to remove the large IgM molecules, and is also recommended when IgM levels are ≥ 60 g/L [79]. Avoidance of red cell transfusions is recommended in this setting; if absolutely necessary, this should be timed to follow plasmapheresis [80]; careful fluid management to prevent exacerbation of hyperviscosity and acute pulmonary oedema is required. Iron infusions may be useful for management of functional iron deficiency secondary to hepcidin excess[81].

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 diuresis 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 hypogammaglobulinemia, 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. Use of intravenous or subcutaneous immunoglobulin therapy should be considered in such patients.

Stem Cell Transplantation

ASCT may 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 [84,85]. Prolonged median PFS of 60 months or more were reported, but these results are not sufficiently superior to those of induction regimens such as DRC and certainly not to BTKi, to justify the cost and toxicity (**Table 6**). ASCT is therefore not recommended in the frontline setting.

Retrospective studies have reported median PFS of 3 – 4 years across a variety of disease stages in relapsed patients [85,86]. 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). There is no data on role of ASCT in the BTKi era; however, ASCT would be a reasonable option in patients with aggressive disease and/or intolerance to BTKi. 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 [87].

Allogeneic stem cell transplantation is used rarely, and is reserved for younger, fit patients with aggressive relapsed or refractory disease or transformed WM, who have a suitable donor and/or are resistant/intolerant to BTKi.

Bing Neel Syndrome

Bing Neel syndrome, so named because it was first observed by Bing and Neel in 1937, is a rare neurologic complication of WM occurring in ~1% of patients. It is 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 [88].

The clinicopathologic entity can occur after or before definitive diagnosis of WM (characterised by BM infiltration and IgM paraproteinemia). Diagnostic criteria developed by the 8th International Workshop on Waldenström Macroglobulinaemia include demonstration of monoclonal lymphoid cells with the characteristic phenotype (using flow cytometry, immunohistochemistry and/or monoclonal IgH) in CSF or on histologic biopsy. Other investigations include testing for MYD88 L265P mutation on CSF, and imaging of the brain and spinal cord using CT and/or MRI [88].

While chemotherapy drugs known to traverse the blood brain barrier such as methotrexate and cytarabine have been used in the past, the dose dependent penetration of the blood brain barrier by BTKi [89] has changed the treatment paradigm. A recent international retrospective study on single agent ibrutinib in 28 BNS patients showed symptomatic and radiologic improvements in 85% and 60% patients respectively within 3 months of treatment. The 2-year EFS rate with ibrutinib was 80% (95% confidence interval [CI], 58%-91%), the 2-year ibrutinib survival rate was 81% (95% CI, 49%-94%), and the 5-year BNS survival rate was 86% (95% CI, 63%-95%) [90]. Based on this study, use of BTKi is recommended for BNS.

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 [29,91] and is characterised by rapidly enlarging lymphadenopathy or extra nodal disease, and rising lactate dehydrogenase. DLBCL occurring in the context of antecedent WM is known to occur from clonal evolution of the underlying WM, but can also occur as an independent clone - because of the worse prognosis associated with transformed disease as compared to de-novo DLBCL, it is suggested that the lymphoma-specific IgH sequence be tracked in the WM clone and transformed tissue [92]. Most cases of transformation involve extra-nodal sites, commonly CNS, cutaneous or testicular [93].

A tissue biopsy is recommended to confirm histological transformation, and tested for EBV as it has been implicated in the pathogenesis, [94,95]. More than 80% of cases have a non-germinal centre B-cell phenotype [93].Often, discordant involvement of the BM with small cells typical of WM is noted. 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.

5 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, which have revolutionised treatment. At the same time, unique aspects of WM management such as IgM flare on cessation of BTKi pose challenges to less experienced clinicians and underscore the need for disease-specific treatment guidelines. Given the rapid advances in WM therapy and the limited 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 International Workshop on WM (IWWM) [105], the second from the National Comprehensive Cancer Network (NCCN) [106]. The IWWM guidelines were published prior to the data on Zanubrutinib being published.

The IWWM guidelines emphasize 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 due to current paucity of evidence;

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

(4) In BTKi naïve patients, BTKi therapy is recommended at relapse.

(4) Salvage therapy after remissions of ≥12 months may include repeat administration of the induction chemo-immunotherapy regimen, especially if BTKi is contraindicated;

(5) Salvage options after shorter remissions include recruitment to clinical trials, BTKi therapy, switching to a different chemotherapy, bortezomib or 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 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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