Christian Buske
Jorge J Castillo
Roger Owen
Shayna R Sarosiek

Oncology
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Hematology

Fast Facts

Waldenström Macroglobulinemia

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Fast Facts for Healthcare Professionals

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Waldenström Macroglobulinemia

Christian Buske MD
Medical Director
Institute for Experimental Cancer Research CCC Ulm
University Hospital Ulm
Ulm, Germany

Jorge J Castillo MD
Clinical Director
Bing Center for Waldenström's Macroglobulinemia
Dana-Farber Cancer Institute
Boston, MA, USA

Roger Owen MRCP MRCPath MD
Consultant Haematologist
St James's University Hospital
Leeds, UK

Shayna R Sarosiek MD
Physician
Bing Center for Waldenström's Macroglobulinemia
Dana-Farber Cancer Institute
Boston, MA, USA

Declaration of Independence
This book is as balanced and practical as we can make it.
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Buske C (Christian)
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Christian Buske, Jorge J Castillo, Roger Owen, Shayna R Sarosiek

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List of abbreviations

ADC: antibody-drug conjugate

AE: adverse event

AF: atrial fibrillation

AL: light-chain (amyloidosis)

BCL2: B-cell lymphoma-2 (antagonist)

bd: twice daily

B-DRC: bortezomib-dexamethasone-rituximab-cyclophosphamide

BiTE: Bispecific T-cell engager

BR: bendamustine-rituximab

BTK: Bruton tyrosine kinase

CAD: cold agglutinin disease

CAR: chimeric antigen receptor

CaRD: carfilzomib-rituximab-dexamethasone

CLL: chronic lymphocytic leukemia

CNS: central nervous system

cp: centipoise

CR: complete response

CSF: cerebrospinal fluid

CT: computed tomography

C-terminus: carboxyl terminus

***CXCR4*:** C-X-C chemokine receptor type 4 (gene)

DLBCL: diffuse large B-cell lymphoma

DOR: duration of response

DRC: dexamethasone-rituximab-cyclophosphamide

EBMT: European Bone Marrow Transplant (registry)

EMA: European Medicines Agency

FDA: Food and Drug Administration

HCK: hematopoietic cell kinase

IDR: ixazomib-dexamethasone-rituximab

IHC: immunohistochemistry

IgM: immunoglobulin M

IPSSM: International Prognostic Scoring System for WM

IRAK1/IRAK4: interleukin-1 receptor associated kinases 1 and 4

LDH: lactate dehydrogenase

LPL: lymphoplasmacytic lymphoma

MAG: myelin-associated glycoprotein

MGUS: monoclonal gammopathy of undetermined significance

MRD: minimal residual disease

MRR: major response rate

mTOR: mammalian target of rapamycin

***MYD88*:** myeloid differentiation 88 (gene)

NF-κB: nuclear factor kappa light-chain enhancer of activated B cells

od: once daily

OR: objective response

ORR: overall response rate

OS: overall survival

PCR: polymerase chain reaction

PD-1: programmed cell death 1 protein

PET: positron emission tomography

PFS: progression-free survival

PI: proteasome inhibitor

PI3K: phosphatidylinositol-3 kinase

PR: partial response

R-CHOP: rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone

RR: response rate

SCT: stem-cell transplantation

SEER: Surveillance, Epidemiology, and End Results

TLS: tumor lysis syndrome

VGPR: very good partial response

WM: Waldenström macroglobulinemia

Introduction

Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma characterized by the presence of an immunoglobulin M (IgM) monoclonal protein. The clinical presentation of WM is varied. Presenting signs and symptoms may be secondary to overall disease burden or related to the unique chemical, physical and immunologic properties of the secreted IgM monoclonal paraprotein that may lead to complications, such as hyperviscosity, cold agglutinin hemolytic anemia, peripheral neuropathy or light-chain (AL) amyloidosis.

WM is a chronic, indolent disease, which can remain undiagnosed for years in some patients. There is no curative therapy, and it is generally recommended that asymptomatic patients with WM are followed closely, with the plan to introduce therapy for disease control when specific treatment criteria are met. Many patients can be actively monitored without therapy for years.

A little over a decade ago, an international prognostic score system was devised for WM and in 2019 this was revised to reflect advances in our knowledge of the disease and its treatment and the resulting increases in survival.

Historically, research has tended to focus on other B-cell lymphoid malignancies, but more recently there has been an upsurge in molecular research in WM. A better understanding of the role of signaling pathways in the development of the disease and the identification of clinical and genetic markers have driven the development of targeted therapeutic strategies, improving overall survival.

In this resource, we distill current knowledge on the pathophysiology, epidemiology and etiology of WM and discuss how the disease may present, how it is diagnosed and when treatment should be initiated. We also provide an overview of current approaches to treatment as well as ongoing and planned research directions. It contains a wealth of information for those working in the field and will be of particular value to specialist nurses and trainees in the fields of hematology, oncology, gerontology, pathology and neurology.

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1 Epidemiology, etiology and overview

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Disease definitions

Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by:

- immunoglobulin M (IgM) monoclonal gammopathy of any concentration
- bone marrow infiltration by lymphoplasmacytic lymphoma (LPL).[1]

IgM monoclonal gammopathy of undetermined significance (MGUS) is a precursor condition defined by:

- IgM monoclonal gammopathy of any size
- absence of LPL bone marrow infiltration
- absence of signs and symptoms.[1]

The term IgM-related disorder denotes the presence of clinical features attributable to the IgM paraprotein, such as peripheral neuropathy, cryoglobulinemia and cold agglutinin disease (CAD), typically in the absence of overt bone marrow infiltration.[1]

Epidemiology

WM is a rare disorder, accounting for only 1–2% of all non-Hodgkin lymphomas.[2] The disease is more common in White than in Black individuals and has an even lower incidence in those of Asian descent.

Overall, the median age at diagnosis is 70 years, though this varies by race: 63 years in Black people compared with 73 years in White people. Additionally, WM is more common in men than in women. Figure 1.1 shows data from 4472 patients of nine Surveillance, Epidemiology, and End Results (SEER) registries between 1980 and 2016. The highest incidence was seen in White men aged 70–79 years.[3] In the USA, there are approximately 1500 new cases of WM each year, with an incidence of 3.4 per million men and 1.7 per million women per year.[4] In Europe, the incidence is slightly higher: 7.3 per million men and 4.2 per million women per year.[5]

Familial clustering. Although WM is thought to be a sporadic disease in most cases, there are familial clusters related to genetic and potentially environmental factors. Patients with familial disease tend to have a higher degree of bone marrow involvement and present at a younger age.[6] Approximately 19% of patients with WM have one

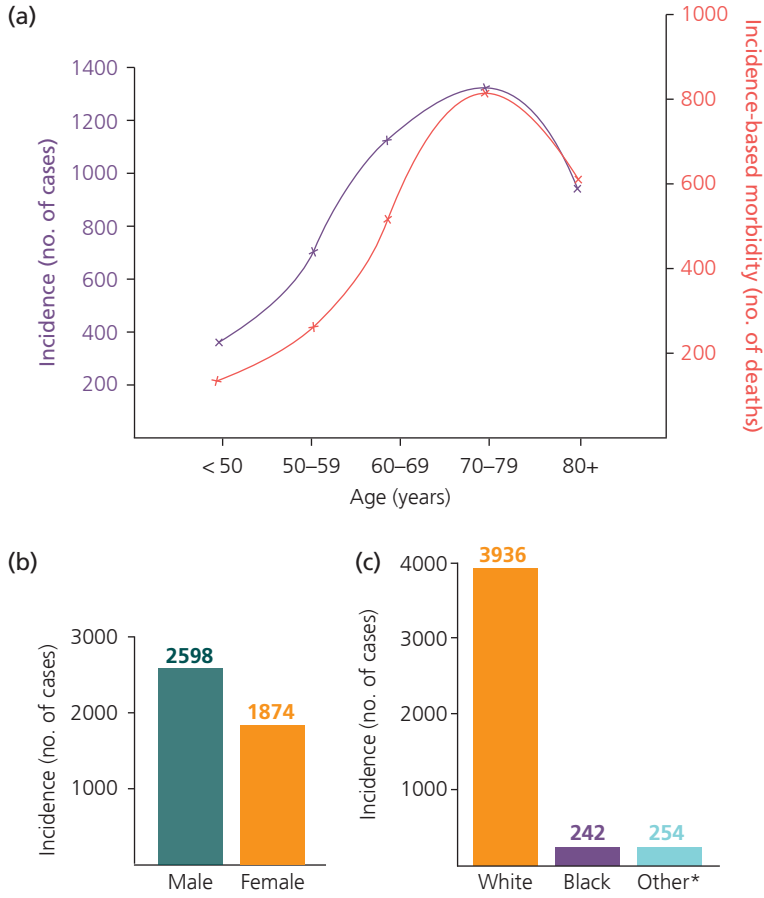

Figure 1.1 Incidence of WM in the USA by (a) age, (b) sex and (c) race from nine SEER registries, 1980–2016; (a) also shows the number of deaths by age during this period. *Includes individuals of American Indian/Alaskan native and Pacific island descent. Adapted from data in Yin et al. 2020.[3]

first-degree relative with WM or another B-cell lymphoproliferative disorder. There is a notable increase in MGUS in first-degree relatives of those with WM. These individuals have up to ten times the risk of MGUS compared with the general population.[7]

Cellular and genetic characteristics

The diagnosis of WM requires the presence of a clonal population in the bone marrow. This population is classically intertrabecular with a spectrum of clonal B cells that includes small lymphocytes as well as LPL cells and plasma cells.[1]

The typical immunophenotype demonstrates expression of either kappa or lambda light chains along with surface IgM, CD19, CD20, CD22, CD25 and CD79a. Cells with plasmacytic differentiation express CD38 and CD138. Although typically absent, CD5, CD10, CD11c and CD23 expression may occur in some cases.

Structural chromosomal abnormalities. The most common one identified in WM is deletion 6q, which occurs in up to 50% of patients with WM.[8,9] The additional chromosomal abnormalities seen most frequently include trisomy 18, 13q deletion, 17p deletion, trisomy 4 and 11q deletion (the site of the *ATM* gene).[9] The prognostic significance of these mutations is still being explored.

Genetic mutations

MYD88. Whole-genome sequencing has revealed that the most common genetic mutation in WM is a single nucleotide change in the myeloid differentiation 88 gene (*MYD88*) that results in a leucine-to-proline change at amino acid position 265.[10] This *MYD88* L265P mutation is seen in 95% or more of patients with WM and results in tumor growth via the activation of nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) by Bruton tyrosine kinase (BTK), as well as through interleukin-1 receptor-associated kinases 1 and 4 (IRAK1/IRAK4) and hematopoietic cell kinase (HCK) (Figure 1.2).[11–13]

Despite the frequency of *MYD88* mutations in WM, the presence of an *MYD88* mutation is not diagnostic, as some other hematologic malignancies, such as marginal zone lymphoma, MGUS or chronic lymphocytic leukemia (CLL), may also harbor an *MYD88* mutation. The 5% of patients with WM who do not have an *MYD88* L265P mutation may have other *MYD88* mutations or may have wild-type *MYD88*. *MYD88* mutational status is known to affect specific factors of the disease, including a higher risk of transformation to an aggressive

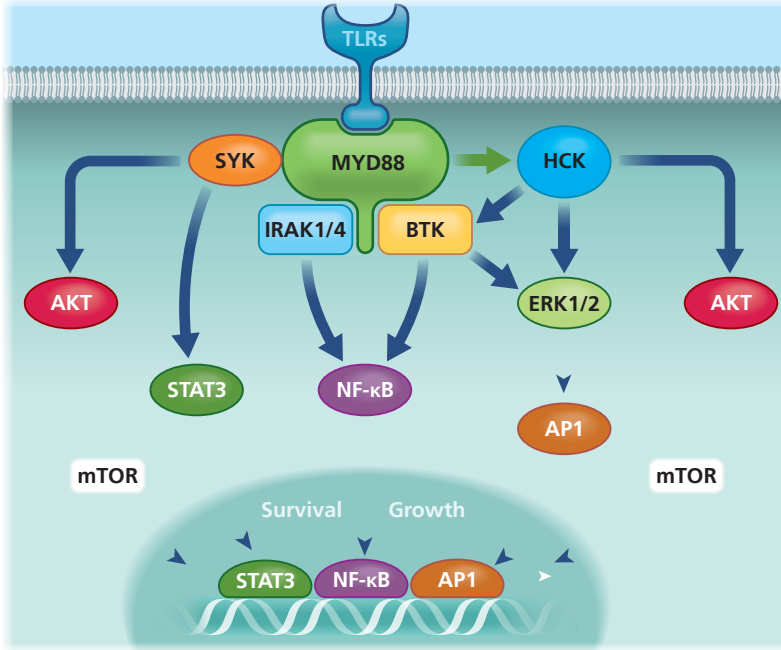

Figure 1.2 Mutated *MYD88* has oncogenic properties. The mutated *MYD88* forms a 'myddosome' with activated BTK and IRAK4/IRAK1. The myddosome activates NF-κB. Mutated *MYD88* also upregulates HCK transcription and transactivates it via interleukin 6. HCK triggers BTK, AKT serine/threonine kinase 1 (AKT1) and extracellular signal-regulated kinase (ERK) activation itself. Mutated *MYD88* also activates spleen tyrosine kinase (SYK), which triggers signal transducer and activator of transcription 3 (STAT3) and AKT. AP1, activator protein 1; mTOR, mammalian target of rapamycin; TLR, toll-like receptor. Simplified from Munshi et al. 2020 (CC BY 4.0).[14]

lymphoma, increased resistance to therapy and possibly worse survival in those with *MYD88* wild-type disease.[15,16]

CXCR4. The second most common somatic mutation described in patients with WM is a mutation in *CXCR4*, which encodes C-X-C chemokine receptor type 4 (CXCR4); about 40% of patients have a *CXCR4* mutation.[17,18] Over 40 different mutations have been

reported.[19] These occur in the carboxyl terminus (C-terminus) and include nonsense (*CXCR4* WHIM/NS) and frameshift (*CXCR4* WHIM/FS) mutations that lead to overactivation of proteins regulating cell growth, as well as increased cell migration, adhesion and survival.[19–21]

Patients with *CXCR4*-mutated disease are known to have lower rates of lymphadenopathy, increased bone marrow involvement, higher serum IgM and a higher risk of hyperviscosity compared with patients with wild-type *CXCR4*.[22] *CXCR4* WHIM/NS mutations have also been associated with lower odds of major response and decreased progression-free survival (PFS) in patients receiving therapy with the BTK inhibitor ibrutinib. Research is ongoing to better characterize the effects of the additional distinct types of *CXCR4* mutation on treatment response and prognosis.[23]

Disease course

WM is often diagnosed incidentally and preceded by MGUS or smoldering (asymptomatic) WM. MGUS is characterized by the presence of an IgM monoclonal paraprotein with a monoclonal spike of any size without evidence of bone marrow infiltration, and absence of any clinical signs or symptoms related to the IgM paraprotein. Smoldering WM is typically defined as the presence of an LPL infiltrate in the bone marrow with an associated IgM monoclonal paraprotein without clinical signs or symptoms of disease.[1] The risk of progression from IgM MGUS to WM is approximately 1–2% per year.[24] In patients with MGUS or smoldering WM, those with the lowest risk of progression have no evidence of immunoparesis and less than 20% bone marrow infiltration of LPL. These patients have a 3% and 6% incidence of progression at 10 and 20 years, respectively.[25]

Predicting progression. Many patients are asymptomatic at the time of WM diagnosis, with a median time to progression from asymptomatic WM to symptomatic WM being measured in years.[15]

Specific risk factors such as albumin, β2-microglobulin, degree of bone marrow infiltration and IgM level can predict progression of disease. A scoring system based on these variables identified three groups of patients with asymptomatic disease with a median time to progression of 1.8, 4.8 and 9.3 years.[15] Importantly, a small subgroup

of patients who have bone marrow infiltration of less than 10% and an IgM below 2000 mg/dL have a PFS rate of 100% and 79% at 5 and 10 years, respectively.[15] *MYD88* mutational status can also affect progression from asymptomatic WM and is an independent risk factor, with those patients with wild-type *MYD88* status having a higher risk of progression to symptomatic disease.[16]

Treatment decisions

With a risk of progression to symptomatic disease of approximately 59% at 5 years and 68% at 10 years, treatment is not always indicated at the time of diagnosis and close monitoring with laboratory tests every 3–6 months is recommended in many patients.[26]

Ultimately, the decision to initiate treatment is based on both clinical and laboratory parameters, with the most common reason for treatment initiation being fatigue, generally related to a hemoglobin below 10 g/dL.[27]

Hyperviscosity. Excess production of IgM and the formation of large pentameric molecules increases blood viscosity. Hyperviscosity symptoms may underlie the decision to initiate treatment in 10–30% of patients.[28] Normal viscosity is 1.4–1.8 centipoise (cp) and symptoms of hyperviscosity can develop when viscosity reaches 4 cp or above. However, viscosity quantified by cp alone correlates poorly with the development of clinical signs of hyperviscosity.

The risk of hyperviscosity increases with IgM level, with the risk of symptomatic hyperviscosity approximately:

- 3% with serum IgM 30.01–40 g/L
- 22% with IgM 40.01–50 g/L
- 32% with IgM 50.01–60 g/L
- 67% with IgM >60 g/L.[29]

Symptoms of hyperviscosity typically include oronasal bleeding, acute visual changes due to retinal hemorrhage, and CNS manifestations such as light headedness, dizziness and fatigue.

Additional indications for treatment include platelets below 100×10^9/L, symptomatic lymphadenopathy or splenomegaly, constitutional symptoms (fevers, unintentional weight loss and

drenching night sweats), progressive symptomatic neuropathy, cryoglobulinemia, cold agglutinin hemolytic anemia or associated light chain (AL) amyloidosis (see Chapter 2).[27]

Prognosis

The median overall survival (OS) in patients with WM differs with age: over 10 years for those under 70, approximately 7 years for those aged 70–79, and approximately 4 years for those aged 80 years or older.[30] Figure 1.3 shows an increase in 5-year relative survival rates for patients with WM in the USA between 1980 and 2010 regardless of age, sex and ethnicity. Most patients with WM have comorbidities that may lead to non-WM-related deaths.[31] OS may also be worse in those patients with familial WM.[32]

Prediction of OS is aided by the International Prognostic Scoring System for WM (IPSSWM), which can be applied to patients who require therapy. Depending on the values, patients can be regarded as low, intermediate or high risk, with predicted median OS of 142.5 months, 98.6 months and 43.5 months, respectively.[33] There is also a modified version of the IPSSWM that includes elevated lactate dehydrogenase (LDH) as another risk factor that informs prediction of survival (see Chapter 2).[34]

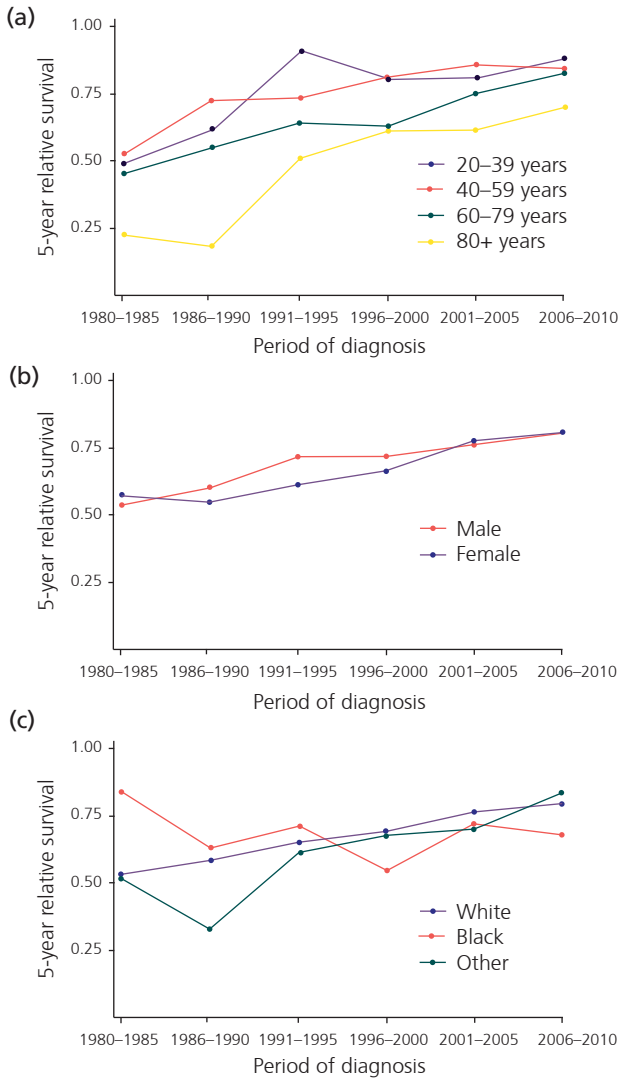

Figure 1.3 Increase in 5-year relative survival in patients with WM from the SEER database (1980–2010) by (a) age, (b) sex and (c) race. Reproduced with permission from Castillo et al. 2014.[30]

Key points – epidemiology, etiology and overview

- WM is a rare subtype of non-Hodgkin lymphoma characterized by an IgM monoclonal paraprotein and an associated LPL bone marrow infiltration.
- *MYD88* L265P is the most common somatic mutation in WM; it is present in more than 90% of patients.
- Numerous *CXCR4* mutations exist, including both frameshift and nonsense mutations, and are detected in approximately 40% of patients. *CXCR4* mutations affect the clinical presentation and can also affect response to therapy.
- Many patients are diagnosed incidentally and treatment may not be necessary at the time of diagnosis. Monitoring every 3–6 months with physical examination, laboratory testing and assessment of symptoms is sufficient.
- Symptomatic anemia is the most common reason for treatment initiation. Additional criteria for treatment include hyperviscosity, symptomatic lymphadenopathy or splenomegaly, constitutional symptoms (including fevers, unintentional weight loss and drenching night sweats), progressive symptomatic neuropathy, cryoglobulinemia, cold agglutinin hemolytic anemia and associated AL amyloidosis.

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2 Diagnostic work-up and prognosis

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Diagnosis requires histopathological confirmation of bone marrow infiltration by LPL in the context of IgM monoclonal gammopathy.

Clinical evaluation

As WM is characterized by a diverse range of clinical features, diagnostic work-up begins with a detailed medical history, physical examination, and symptom and systems review (Table 2.1). It is also important to ask about family history of WM and other B-cell lymphoproliferative disorders.

Basic investigations for the evaluation of presenting patients include:

- full blood count
- serum protein electrophoresis and immunofixation
- quantification of IgM by densitometry
- quantification of IgG and IgA
- urea and creatinine
- liver function tests
- LDH
- β2-microglobulin.

TABLE 2.1

Signs and symptoms of WM

- B symptoms
  - Unexplained fever, night sweats, unintentional weight loss
- Organomegaly and lymphadenopathy
- Hyperviscosity symptoms
  - Light-headedness, dizziness, fatigue, headaches, blurred vision or vision loss, confusion, hypertension, epistaxis, thrombosis, heart or kidney failure
- Neuropathy
- Raynaud phenomenon
- Rash and other skin abnormalities
- Peripheral edema
- Dyspnea

Additional investigations may be required, depending on the medical history and symptoms (Table 2.2).

Anemia is the most common presenting symptom and while this may reflect bone marrow infiltration and/or a dilutional effect in those with high paraprotein levels, alternative causes should always be considered. These include autoimmune hemolysis, CAD and functional iron deficiency. The last has been described in WM as a consequence of hepcidin overproduction, possibly by lymphaplasmacytic cells.[1]

TABLE 2.2

Additional investigations after basic test results

Symptoms	Basic investigations	Further investigations
Fatigue	Reduced hemoglobin	• Blood film • Hematinics, including transferrin saturation • Reticulocyte count • Direct antiglobulin test • Cold agglutinin titer
Sensory symptoms in hands and feet		• MAG antibodies • Nerve conduction studies • Neurology consult
Headaches, blurred vision, confusion, epistaxis	Paraprotein >30g/L	• Ophthalmic assessment* • Plasma/serum viscosity *Consider Bing–Neel syndrome if no evidence of hyperviscosity*
Cold-induced symptoms (acrocyanosis, Raynaud phenomenon)		• Blood film • Direct antiglobulin test • Cold agglutinin titer • Cryoglobulin screen • Complement *Consider CAD/cryoglobulinemia*

CONTINUED

TABLE 2.2 CONTINUED

Additional investigations after basic test results

Symptoms	Basic investigations	Further investigations
Bruising and/or bleeding	Thrombocytopenia	• Clotting screen • von Willebrand screen *Consider immune thrombocytopenia and acquired von Willebrand disease*
Peripheral edema	Renal impairment Proteinuria Low serum albumin	• 24-hour urinary protein • Serum free light chains • Renal consult *Consider monoclonal gammopathy of renal significance and AL amyloidosis*
Skin problems (petechiae, skin ulcers, urticaria)		• Cryoglobulin screen • Complement • Dermatology / immunology consults *Consider cryglobulinemia and Schnitzler syndrome*

*Clinically relevant hyperviscosity will present as retinal hemorrhage and/or retinal vein engorgement. A baseline photograph is useful for future comparisons, bearing in mind abnormalities that may present because of comorbidities such as arterial hypertension or diabetes.
MAG, myelin-associated glycoprotein.

IgM assessments

IgM paraproteins should be demonstrated by serum protein electrophoresis and immunofixation and quantitated by densitometry (Figure 2.1). Assessment of total IgM concentration by nephelometry is an alternative to densitometric assessment of paraprotein concentration, although the former provides systematically higher values. IgG and IgA should also be determined at diagnosis and at regular intervals during follow up.

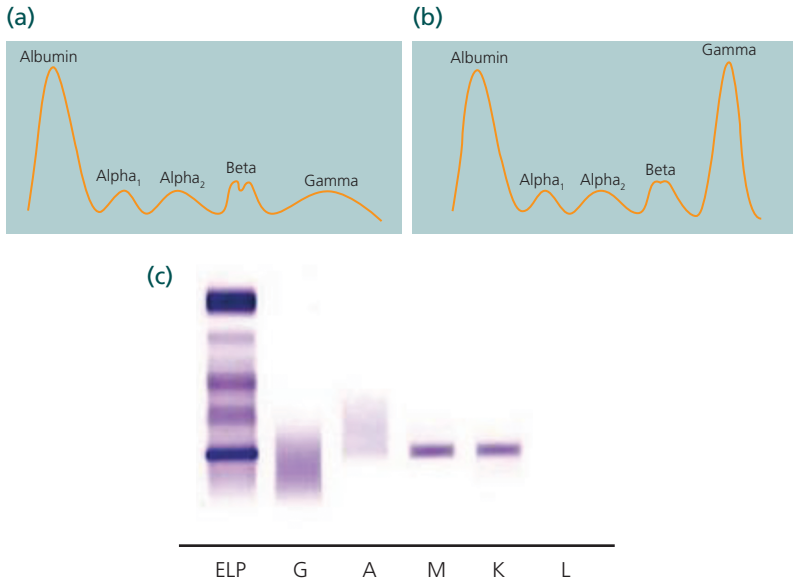

Figure 2.1 (a) Normal serum protein electrophoresis compared with (b) homogenous spike in the gamma-globulin region, indicating the presence of a monoclonal gammopathy. (c) Immunofixation identifies the type of immunoglobulin as IgM, with a well-defined band reactive to anti-IgM (M), and a similar band for anti-kappa (K) identifies the clonality of the light chain. ELP, electropherogram.

Cellular synthesis of paraprotein is relatively constant in an individual patient, so the concentration of paraprotein indicates tumor burden. It is therefore essential that sequential assessments of paraprotein/IgM concentration be performed by the same method and ideally within the same laboratory.

The serum free light chain (SFLC) assay is of limited value in routine practice; its clinical utility is limited to those rare patients with light chain-associated pathology such as cast nephropathy, renal gammopathy and AL amyloidosis.[2]

Pathological diagnosis and genomic assessment

The presence of an IgM paraprotein in isolation, regardless of concentration, is not indicative of WM as it is also seen in patients

with MGUS and other B-cell lymphoproliferative disorders, with considerable overlap in serum concentrations.[3]

Detailed morphological and immunophenotypic assessment of the bone marrow with close clinical correlation is therefore required for a definitive diagnosis of WM. Bone marrow assessment is recommended in all patients suspected of having symptomatic WM or an IgM-related disorder.[2] The value of assessment in asymptomatic individuals has not been established but may provide prognostic information about the risk of progression, which can be discussed with individual patients.[4]

Immunohistochemistry. LPL is characterized by the following morphological features:[5]

- plasma cell differentiation
- increased reactive mast cells
- immunoglobulin inclusions (Russell and Dutcher bodies)
- non-paratrabecular infiltration pattern.

Plasma cell differentiation is an important morphological feature, readily appreciated on trephine biopsy sections, and can be further accentuated with immunohistochemistry (IHC) using plasma cell-specific antibodies such as CD138 and/or IRF4 (Figure 2.2). The extent of plasma cell differentiation varies and appears to correlate better with IgM concentrations than overall bone marrow disease burden.[6]

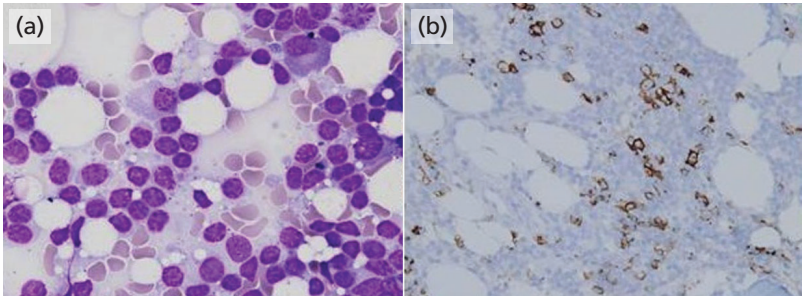

Figure 2.2 (a) Bone marrow aspirate showing an increased number of small lymphocytes, together with LPL and plasma cells. Wright-Giemsa stain × 1000. (b) Scattered plasma cells show positivity for CD138. CD138 IHC stain × 400.

Immunophenotypic studies are necessary for a definitive diagnosis of WM and this may be achieved using either flow cytometry or IHC, although the former provides a more extensive assessment of antigenic determinants. It is generally possible to demonstrate both monotypic B cells and monotypic plasma cells, but extended phenotyping is usually only performed on the B-cell component. The B cells in WM have the following immunophenotypic profile:[7]

- expression of pan B-cell antigens CD19, CD20 and CD79a
- expression of CD25, CD27 and IgM along with weak CD22
- absence of CD5, CD10, CD11c, CD23 and CD103 in many cases.

The pattern of expression of CD22 and CD25 appears relatively specific to WM and provides a robust basis on which to make a diagnosis and differentiate the disease from marginal zone lymphoma, which frequently has a $CD22^{+}$ $CD25^{-}$ $CD103^{+}$ immunophenotype. Flow cytometric evaluation of B cells for these phenotypic determinants is a useful adjunct in the assessment of patients with IgM-related disorders, which are typically characterized by a low disease burden.

Genomic profiling. Whole-genome sequencing has shown that more than 90% of patients with WM harbor a single point mutation in *MYD88*, the L265P mutation. This appears central to WM pathogenesis and leads to downstream activation of NF-κB via divergent pathways including BTK and IRAK1/IRAK4 (see Figure 1.2).[8,9]

Although not specific to WM, detection of *MYD88* L265P has clear diagnostic utility, allowing for precise genomic diagnosis in the correct clinical and pathological context. There is no clear consensus on methodologies, although allele-specific polymerase chain reaction (PCR), digital droplet PCR and high-throughput sequencing have all been described.[10–12] Laboratories should establish and report the sensitivity of their assays so that results may be correlated with the level of bone marrow disease assessed by morphology and flow cytometry.

Mutation of *CXCR4* is seen in 30–40% of patients with WM and involves the carboxyl terminal of the gene that is responsible for regulating signaling following ligation with SDF-1a (CXCL12). A number of truncating nonsense and frameshift mutations have been described and are similar to those seen in the WHIM immunodeficiency syndrome. *CXCR4* mutations are subclonal with

variable allele frequencies and some patients may acquire multiple mutations.[13–15] The utility of *CXCR4* assessment has not been fully established in routine clinical care. Indeed, the subclonal nature and diversity of *CXCR4* mutations present a considerable challenge to laboratories. While there is a mutation hotspot at S338 (suitable for relatively simple allele-specific oligonucleotide [ASO]-PCR approaches) it seems likely that high-throughput sequencing technologies following B-cell selection will provide the optimal approach.[15,16]

TP53 abnormalities (17p deletion and/or gene mutation) are noted in up to 10% of patients with WM and are associated with inferior survival outcomes.[17] Assessment of *TP53* is not routine practice but could influence some treatment decisions. B-cell selection and high-throughput sequencing approaches are considered optimal for detecting *TP53* mutations.

Imaging

Lymphadenopathy and splenomegaly are infrequent in patients with WM, being reported in approximately 15% of patients before treatment, but become more common as disease progresses. Baseline CT imaging is standard practice in symptomatic patients before starting therapy.[2] There are limited data on the utility of fluorodeoxyglucose (FDG)-PET scanning, but it may have a role in assessing patients with suspected histological transformation.

Prognostic assessment

The IPSSWM is based on assessment of five adverse prognostic features at the time of treatment:

- age > 65 years
- hemoglobin concentration < 11.5 g/dL
- platelets ≤ 100×10^9/L
- β2-microglobulin > 3 mg/L
- monoclonal IgM concentration > 70 g/L.

This system defines three risk groups with a 5-year OS of 87%, 68% and 36%.[18] A modified IPSSWM that defines five risk groups has also been proposed (Table 2.3).[19]

There is consensus that these scoring schemas should be recorded in clinical trials to allow between-trial comparisons, but there is no evidence that they influence treatment decisions for individual patients.

TABLE 2.3

Revised IPSSWM: criteria and risk stratification[19]

Criterion	Score	
Age ≤ 65	0	
Age 66–75 years	1	
Age ≥ 76 years	2	
β2-microglobulin ≥ 4 mg/L	1	
LDH ≥ 250 IU/L (ULN < 225)	1	
Serum albumin < 3.5 g/dL	1	
Risk group (total score)*	**3-year WM-related death rate**	**10-year OS**
Very low (0)	0%	84%
Low (1)	10%	59%
Intermediate (2)	14%	37%
High (3)	38%	19%
Very high (4–5)	48%	9%

*Sum of individual criterion scores. ULN upper limit of normal.

A prognostic scheme, requiring bone marrow assessment, has also been developed to predict risk of progression in asymptomatic patients (www.awmrisk.com).[4]

The impact of genomic profiles on survival outcomes is not yet fully established. Some studies suggest that wild-type *MYD88* disease has a greater risk of histological transformation (see below), poor outcomes with ibrutinib and inferior OS.[20,21] A large retrospective study at the Mayo Clinic did not confirm inferior OS for patients with wild-type disease, while a recent prospective study demonstrated meaningful clinical activity for zanubrutinib.[22,23] *CXCR4* mutations appear to be associated with inferior response rates (RR) and depth of response and shorter PFS with ibrutinib, although this may be overcome with the addition of rituximab.[21,24] As described above, *TP53* mutation, although rare, is associated with inferior OS.[17]

Histological transformation

Histological transformation, primarily to diffuse large B-cell lymphoma (DLBCL), is a well-recognized phenomenon that has been reported in 5–10% of patients with WM. The development of bulky, rapidly enlarging lymph-node masses, extranodal disease and elevated serum LDH are all clinical features seen with transformation.

In a cohort of 77 patients, the median time from diagnosis to high-grade transformation was 4.6 years and 16 patients (21%) had never been treated for WM.[25] Tissue biopsy is essential for diagnosis of histological transformation and may be directed by PET/CT scanning. The pathological features are similar to those seen in de novo DLBCL and a non-germinal center phenotype is typically seen. Epstein–Barr virus-associated DLBCL and mucocutaneous ulcer have been rarely described in WM and are thought to be clonally unrelated and not considered as transformation events. They are likely to occur because of both disease- and treatment-related immune deficiency.[26]

Specific clinical scenarios

Peripheral neuropathy. Approximately 30% of patients with WM have peripheral neuropathy at the time of diagnosis and up to 50% of patients are affected during the course of the disease.[27] Nerve conduction studies can determine the pattern (demyelinating, axonal or mixed) and extent of nerve damage. In WM, the binding of IgM paraprotein to neural targets, such as myelin-associated glycoprotein (MAG), presents as distal, chronic, symmetric and demyelinating polyneuropathy.

Patients with neuropathy should be tested for MAG-directed antibodies. An anti-MAG titer greater than 70 000 BTU (Buhlmann titer units) is indicative of IgM-related neuropathy.

If the anti-MAG titer is negative, further tests should be performed for antibodies against other neural targets, such as gangliosides, sulfatides or oligosaccharides.

If the clinical and electrophysiological findings do not indicate WM as the cause, other pathologies such as cryoglobulinemia or AL amyloidosis (see below) should be investigated. Other causes of peripheral neuropathy, such as diabetes, thyroid dysfunction or nutritional deficiencies, should also be ruled out.

Cold-agglutinin disease. In CAD, the monoclonal IgM has binding specificity for Ii red blood cell antigens and results in complement-mediated hemolysis and cold-induced symptoms such as acrocyanosis and Raynaud phenomenon.[28] The diagnostic features are:

- chronic anemia with red blood cell agglutination on blood film
- direct antiglobulin test (DAT) strongly positive for C3d
- cold agglutinin titer >1 in 64
- low-level bone marrow infiltration.

Most patients have morphological evidence of bone marrow infiltration, but infiltration is low and monoclonal B cells are usually demonstrable by flow cytometry in patients lacking morphological evidence of disease.[28] Evidence suggests that there are immunophenotypic and genotypic differences between WM and CAD. CAD B cells have higher levels of CD5, CD11c, CD23, CD39 and CD200 expression on flow cytometry along with lower levels of CD19, CD79 and IgM compared with WM B cells. There also appears to be a considerably lower incidence of the *MYD88* L256P mutation.[28,29]

Cryoglobulinemia is the presence of circulating cryoglobulins (immunoglobulins that precipitate at temperatures below normal body temperature and redissolve on warming) in the serum. Type 1 (monoclonal) or type II (monoclonal and polyclonal) cryoglobulinemia can occur in patients with WM, but it is symptomatic in only a minority of cases.[30] Clinical features include Raynaud phenomenon, acrocyanosis, purpura, peripheral neuropathy and glomerulonephritis. Serum samples of patients suspected of having cryoglobulinemia should be kept in a warm bath to avoid cryoprecipitation.

AL amyloidosis. In about 3% of patients with WM, an unstable monoclonal IgM and/or light chain may be produced. These unstable proteins can misfold and aggregate into insoluble β-pleated sheets of amyloid fibrils, which are then deposited in tissues and organs. The kidneys, peripheral and autonomic nervous system, lungs, lymph nodes and heart are commonly affected in patients with WM.[31] Untreated progressive systemic AL amyloidosis can lead to multiorgan failure and death.

Diagnosis requires:

- early detection of amyloid-related organ damage
- histological confirmation of amyloid deposits
- accurate amyloid typing.

The most common sign of renal involvement by amyloidosis is albuminuria, which typically precedes development of renal failure. Loss of sensation or progressive symmetric numbness, or tingling or pain in the extremities may indicate peripheral neuropathy. Orthostatic hypotension or gastrointestinal dysmotility may be a sign of autonomic dysfunction. Symptoms of congestive heart failure or elevation in cardiac biomarkers, such as NT-proBNP and troponin, may be a result of cardiac amyloidosis.

If amyloidosis is suspected, tissue biopsy is essential either of the involved organ or of a surrogate site such as abdominal subcutaneous fat or bone marrow. A Congo red stain is utilized to confirm the presence of amyloidosis: amyloid fibrils will produce a characteristic green birefringence when viewed under polarized light. Once amyloid is identified, subtyping must be performed in a specialist laboratory to confirm the subtype of amyloidosis.[32]

Bing–Neel syndrome describes the secondary involvement of the CNS in WM, a rare complication that occurs in about 1% of patients. It usually occurs as a disease progression event in patients with an established diagnosis, but it can also be the presenting feature.[33] Clinical features are diverse, and the following investigations should be considered in patients with unexplained central neurological symptoms:

- brain and whole-spine MRI with gadolinium contrast enhancement
- cerebrospinal fluid (CSF) examination using flow cytometry for WM B cells and/or molecular assessment of *MYD88* L265P.

CSF examination may be uninformative in which case meningeal or parenchymal brain biopsies may be required for definitive diagnosis.

IgM plasma cell myeloma. In some patients with WM (up to 20% in some series), the degree of plasma cell differentiation may be such that plasma cells are the predominant cell type and IgM myeloma becomes part of the differential diagnosis.[34] Although rare, it is essential that a correct diagnosis is made given the poor clinical outcome in IgM myeloma and the availability of targeted therapies in WM.

IgM myeloma is characterized by:[35,36]

- high proportion of skeletal bone lytic lesions
- absence of a $CD20^+$ IgM^+ B-cell component
- aberrant plasma cell phenotype: for example, lack of CD19 and expression of CD56 and cyclin D1
- high incidence of the *CCND1-IGH* translocation
- absence of *MYD88* L265P.

Key points – diagnostic work-up and prognosis

- WM, which is characterized by a broad range of clinical features, requires taking detailed individual and family medical histories and a general systems review as part of the diagnostic work-up.
- Detailed morphological and immunphenotypic assessment of bone marrow by flow cytometry or IHC are required for a definitive diagnosis. Though not solely indicative of WM, IgM paraproteins should be demonstrated as well as IgG and IgA concentrations at diagnosis and at regular intervals during follow-up.
- Baseline CT for lymphadenopathy and splenomegaly should be standard practice before starting therapy.
- Prognosis is based on the IPSSWM, a prognostic scoring system that defines three risk groups with 5-year OS of 87%, 68% and 36%, respectively. A revised system has been proposed with five risk groups and 3-year WM-related death rates of 0%, 10%, 14%, 38% and 48%, respectively, and 10-year OS rates of 84%, 59%, 37%, 19% and 9%.

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Oncology
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Hematology

3 Treatment

HEALTHCARE

When to treat

Asymptomatic patients with WM are not treated but, like patients with other indolent B-cell lymphomas, undergo active monitoring without intervention. There are no data indicating any survival benefit of immediate treatment compared with delaying treatment until emergence of lymphoma-related symptoms or complications.

IgM level alone is not an indication to start treatment, but there is consensus that symptoms caused by circulating IgM paraprotein are cause for initiating treatment (Table 3.1). An IgM level above 50–60 g/L is associated with a higher risk of hyperviscosity and also justifies treatment initiation.

Treatment options

There is no standard treatment for WM. Instead, a range of options allow first-line treatment to be personalized according to the patient's fitness, disease characteristics and personal preferences, while treatment of relapsed patients depends on their fitness, duration of response to first-line treatment and the nature of previous treatments (see Treatment algorithms, pages 52–4).

TABLE 3.1

Symptoms that warrant initiation of treatment

- Anemia (hemoglobin < 10 g/dL)
- Thrombocytopenia (platelets < 100×10^9/L)
- Symptomatic hyperviscosity
- Lymphadenopathy compressing vital organs
- Symptomatic organomegaly
- Peripheral neuropathy
- AL amyloidosis
- Symptomatic cryoglobulinemia
- Symptomatic CAD
- Recurrent B symptoms (fever, night sweats, weight loss)

The toxicity of the regimen should also be considered. Given the indolent, non-curative nature of the disease, the aim of treatment is to control disease without compromising quality of life, de-escalating treatment if necessary (for example, in patients with comorbidities). As WM is a rare disease, patients should be encouraged to enroll in clinical trials when they are available.

Plasmapheresis

Plasmapheresis should be given before or concomitantly with systemic therapy for the immediate relief of symptomatic hyperviscosity, which can be life-threatening. Plasmapheresis can also be considered for rapid control of symptoms associated with CAD or cryoglobulinemia. It should also be considered before treatment with rituximab or ofatumumab for symptomatic patients or asymptomatic patients with an IgM greater than 40 g/L to avoid the complications of rituximab-related IgM flare (see below).

Rituximab monotherapy

Before the introduction of the BTK inhibitor ibrutinib (see page 46), the CD20-directed monoclonal antibody rituximab was the most frequently used chemotherapy-free approach to WM in the USA. Its advantages include low toxicity and a timely fixed duration of treatment; its disadvantages include late responses, overall moderate activity and induction of 'IgM flare', a rapid but transient increase of IgM serum levels.[1] For this reason, single-agent rituximab is not recommended in patients with high IgM levels at risk of hyperviscosity. The risk of IgM flare is lower (~10%) when rituximab is given alongside chemotherapy or ibrutinib. The first cycle of rituximab-chemotherapy or the first 4 weeks of rituximab-ibrutinib can be given without rituximab if there are concerns.

Rituximab monotherapy, which can be administered intravenously or subcutaneously, is still an option for elderly patients with comorbidities or those who cannot tolerate rituximab-chemotherapy or BTK inhibitors. Four-weekly infusions of rituximab monotherapy achieve overall RRs of about 20–30%. However, extended rituximab treatment enhances response rates up to 50%.[2]

Immunochemotherapy

Despite the introduction of BTK inhibitors, rituximab-chemotherapy is still a cornerstone of WM treatment. There are two widely used regimens: dexamethasone-rituximab-cyclophosphamide (DRC) and bendamustine-rituximab (BR). Purine nucleoside analogs, such as fludarabine or cladribine, are less preferred because of severe toxicity but may be used in the late relapse setting. R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone) is also not considered a first choice because of neurotoxicity.

DRC. Dexamethasone, 20 mg, followed by rituximab, 375 mg/m^2, given intravenously on day 1, and cyclophosphamide, 100 mg/m^2, given orally twice daily (bd) on days 1–5, was highly effective in a Phase II trial in 72 previously untreated patients with symptomatic WM. The objective response (OR) on an intent-to-treat basis was 83%, including 7% with complete response (CR), 67% with partial response (PR) and a median time to response of 4.1 months. Two-year PFS for the total patient group was 67%, and 80% in responding patients. This remarkable result was accompanied by only moderate myelotoxicity, with only 9% of patients experiencing grade 3 or 4 hematologic neutropenia and none experiencing grade 3 or 4 thrombocytopenia.[3] The final trial analysis after a median follow-up of 8 years confirmed the favorable toxicity profile and high activity of this immunochemotherapy. Median PFS was 35 months (95% CI 22, 48) and median OS was 95 months (95% CI 87, 103); OS varied with age (Figure 3.1).[4]

BR. Bendamustine, a chemotherapeutic drug, displays characteristics of a purine nucleoside analog and an alkylating agent. Efficacy data are based on subgroup analysis of a German multicenter, open-label, non-inferiority trial, which randomized patients with newly diagnosed stage III or IV indolent or mantle-cell lymphoma between R-CHOP and BR (bendamustine, 90 mg/m^2, on days 1 and 2 of a 4-week cycle) for a maximum of 6 cycles. The primary endpoint was PFS, with a non-inferiority margin of 10%. Patients were assigned to BR (261 of 274 assessed) and R-CHOP (253 of 275 assessed). At a median follow-up of 45 months, median PFS was significantly longer

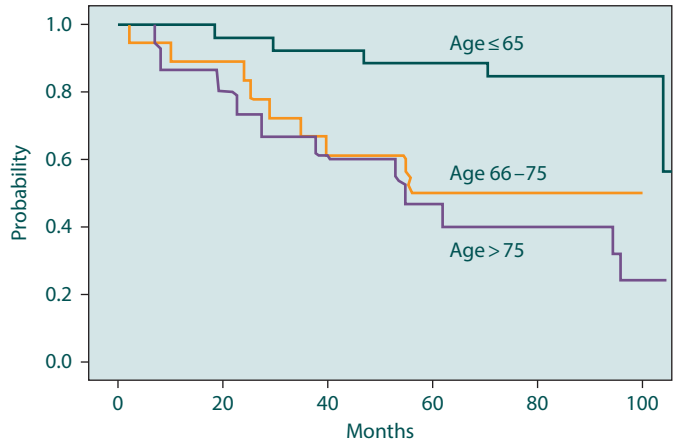

Figure 3.1 OS according to age in patients with symptomatic WM who received first-line DRC chemoimmunotherapy. Median OS was 95 months. Reproduced from Kastritis et al. 2015, with permission of Elsevier.[4]

in the BR arm than the R-CHOP group: 69.5 vs 31.2 months (HR 0.58; $p<0.0001$).[5]

BR had a different toxicity profile to R-CHOP with lower rates of alopecia, less myelotoxicity, and fewer infections and peripheral neuropathy. A subgroup analysis of 41 evaluable patients with WM documented high RR in both arms: 96% for BR and 94% for R-CHOP.[6] Neither treatment regimen induced complete remission.

In a Phase II study of 30 patients with relapsed/refractory WM after bendamustine-containing therapy, 24 received BR, and 4 and 2 rituximab-intolerant patients received single-agent bendamustine and ofatumumab, respectively, over a median of 5 cycles. Overall response rate (ORR) was 83.3%, with very good partial response (VGPR) in 5 patients and PR in 20. The median estimated PFS for all patients was 13 months. Prolonged myelosuppression occurred in 4 patients, 3 of whom had been previously treated with nucleoside analogs.[6]

As with fludarabine, bendamustine induces severe T-cell depletion. In a large randomized trial, bendamustine in combination with rituximab or obinutuzumab was associated with high rates of severe infection and mortality in patients with follicular lymphoma and

marginal zone lymphoma.[7] Given the high rate of *Pneumocystis jiroveci* pneumonia reported in these patients, antiviral and antibacterial prophylaxis should also be considered in patients with WM.

Proteasome inhibitors

The action of proteasome inhibitors results in an accumulation of ubiquitinated proteins and dysregulation of multiple pathways within the cell, ultimately causing apoptosis.

Bortezomib has demonstrated its efficacy as a single agent in patients with WM in several Phase II trials.[8–10] More recently, a combination of bortezomib and rituximab was analyzed in a Phase II trial: 37 patients with relapsed/refractory WM were treated with bortezomib, 1.6 mg/m^2, on days 1, 8 and 15 of a 28-day cycle for 6 cycles, and rituximab, 375 mg/m^2, on days 1, 8, 15 and 22 for cycles 1 and 4. After a median of three treatments, 78% of patients completed treatment. This combination induced an OR of 81% with 5% CR and 46% PR. Grade 3 or 4 toxicity was acceptable with 16% leucocytopenia, 11% anemia and 5% neuropathy. One patient died of pneumonia, emphasizing that severe infectious complications occur in this patient population.[11]

The same regimen was tested in 26 patients with untreated WM, producing 88% minor responses, 58% PR and 8% CR or near-CR. One-year event-free survival was 79% and, importantly, no grade 3 or 4 neuropathy was documented.[12] A lower incidence of peripheral neuropathy was observed using once-weekly bortezomib compared with the grade 3 neuropathy (30%) seen in a study utilizing a twice-weekly schedule of bortezomib, 1.3 mg/m^2.[12] The impact on PFS of once- versus twice-weekly bortezomib remains to be clarified.

Whether bortezomib acts independently of the *MYD88* and *CXCR4* mutational status is still an open question. Prospective data are lacking, but in a retrospective analysis of 63 patients with WM treated with bortezomib-rituximab in the first-line or relapsed/refractory setting as part of a Phase II clinical trial (weekly bortezomib, 1.6 mg/m^2, i.v. on days 1, 8 and 15 every 28 days for 6 cycles, and rituximab, 375 mg/m^2, on days 1, 8, 15 and 22 of cycles 1 and 4), PFS and OS were independent of the *CXCR4* mutational status; all patients carrying the *CXCR4* mutation also had *MYD88* L265P.[13]

The addition of dexamethasone to bortezomib-rituximab (BDR) may have value in patients with adverse prognostic factors as a fixed-duration regimen with a favorable long-term toxicity profile. In a multicenter Phase II study, 59 previously untreated patients with WM received the following BDR 23-week regimen: single-agent intravenous bortezomib, 1.3 mg/m^2, on days 1, 4, 8 and 11 of a 21-day cycle, followed by weekly intravenous bortezomib, 1.6 mg/m^2, on days 1, 8, 15 and 22 for 4 additional 35-day cycles, plus intravenous dexamethasone, 40 mg, and rituximab, 375 mg/m^2, on cycles 2 and 5. OS at 7 years was 66%, with a median PFS of 43 months.[14]

Other proteasome inhibitors. To avoid the neurotoxicity of bortezomib, several trials have explored the feasibility of second-generation proteasome inhibitors such as carfilzomib or ixazomib. Carfilzomib has shown remarkable activity in combination with dexamethasone and rituximab (CaRD) in a small Phase II study in treatment-naive and relapsed patients with WM. CaRD consisted of intravenous carfilzomib, 20 mg/m^2 (cycle 1) and 36 mg/m^2 (cycles 2–6), dexamethasone, 20 mg, on days 1, 2, 8 and 9, and rituximab, 375 mg/m^2, on days 2 and 9 every 21 days, followed by maintenance CaRD every 8 weeks for 8 cycles. This regimen induced an ORR of 87.1% and was not affected by patients' *MYD88* L265P or *CXCR4* WHIM mutation status. Overall, the treatment was well tolerated with some hyperlipasemia, reversible neutropenia and cardiomyopathy in 1 patient (3.2%) with multiple risk factors, and grade 2 peripheral neuropathy in 1 patient (3.2%).[15]

Ixazomib was tested in combination with dexamethasone and rituximab (IDR) in 26 treatment-naive patients with WM. IDR was administered as 6-monthly induction cycles followed by 6 maintenance cycles every 2 months. This regimen induced fast responses with a median time to response and time to major response of 2 and 6 months, respectively. Anti-lymphoma activity was high with ORR, major response and VGPR of 96%, 77% and 19%, respectively. Median PFS was 40 months, median duration of response (DOR) was 38 months, and median time to next treatment (TTNT) was 40 months. Importantly, PFS and DOR were not affected by *CXCR4* mutational status. The safety profile was excellent, with no grade 4 adverse events (AEs) or deaths to date.[16] Taken together, these data demonstrate that

proteasome inhibitors are highly effective and well-tolerated drugs in WM.

BTK inhibitors

Activation of the BTK pathway is an essential mechanism that provides survival advantage to malignant *MYD88*-mutated WM cells (see Figure 1.2).[17] BTK inhibition induces potent cell killing in WM cell lines and primary WM cells, providing a strong scientific rationale for the clinical development of BTK inhibitors for the treatment of patients with WM.

Ibrutinib is the first-in-class oral covalent BTK inhibitor, approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and other regulatory agencies, for the treatment of patients with symptomatic WM. In the USA, ibrutinib was approved without restrictions in both the first-line and relapsed settings. In Europe, ibrutinib was approved without restrictions in relapsed patients, but can only be used as upfront therapy if the patient is ineligible for first-line chemoimmunotherapy.

Ibrutinib, 420 mg once daily (od), was initially evaluated in 63 previously treated patients with WM in a seminal multicenter Phase II study.[18] With a median follow-up of 19 months, the ORR was 91%, the major response rate (MRR) was 73% and 16% of patients had a VGPR. The estimated 24-month PFS was 69%. In the final report, with a median follow-up of 59 months, the MRR increased to 79%, with 30% of patients having a VGPR.[19] Median PFS was not reached and 5-year PFS was 54% (Figure 3.2). *CXCR4* mutations were associated with lower rates of response and shorter PFS. MRRs were 68% and 97%, VGPR 9% and 47%, and 5-year PFS 38% and 70% in patients with and without *CXCR4* mutations, respectively. None of the patients without *MYD88* mutation attained a major response or VGPR. These long-term data support ibrutinib as one of the most active agents in *MYD88*-mutated WM. Grade 3 or higher AEs included neutropenia, thrombocytopenia, infections and anemia. The incidence of atrial fibrillation (AF) was 10%.

Similar results were reported in the open-label substudy of the iNNOVATE trial, in which 31 patients with WM who were refractory to rituximab were treated with ibrutinib.[20] Patients had an ORR of 90%, MRR of 71% and 18-month PFS of 86%. No unexpected AEs were reported.

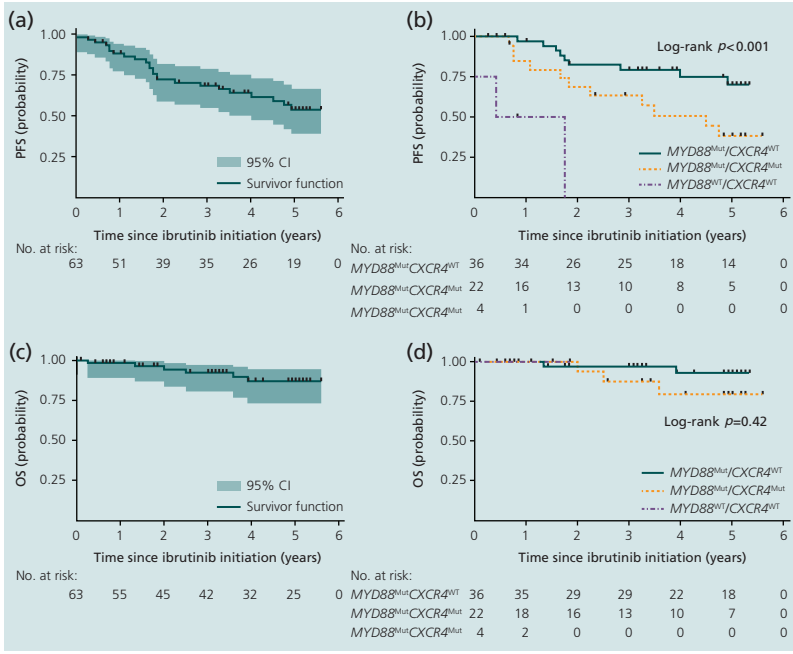

Figure 3.2 Kaplan–Meier curves for 63 previously treated patients with WM after ibrutinib monotherapy. (a) PFS; (b) PFS by *MYD88* and *CXCR4* mutation status; (c) OS; (d) OS by *MYD88* and *CXCR4* mutation status. Reproduced with permission from Treon et al. 2021.[19] © 2020 American Society of Clinical Oncology. https://ascopubs.org/doi/10.1200/JCO.20.00555

Ibrutinib was also evaluated in 30 treatment-naive patients with WM. At a median follow-up of 15 months patients demonstrated 100% ORR, 83% MRR, 20% VGPR and an estimated 18-month PFS of 92%.[21] Grade 3 AEs were thrombocytopenia, bleeding, increase in serum liver enzyme levels and hypertension.

Ibrutinib-rituximab. A combination of ibrutinib and rituximab was compared with placebo and rituximab in the iNNOVATE main study that randomized 150 patients with WM 1:1 to each arm.[22] At a median follow-up of 50 months, median PFS was significantly longer in the ibrutinib-rituximab arm than the placebo-rituximab arm regardless of genotype or prior treatment status (not reached vs 20.3 months; HR 0.25; 95% CI 0.15, 0.42; $p<0.0001$). ORRs were 92% vs 44% and

MRRs were 76% vs 31% for ibrutinib-rituximab and placebo-rituximab, respectively. Infections and infestations, anemia, hypertension and AF were the most common grade 3 or higher AEs with ibrutinib-rituximab; infusion-related reactions and IgM flares were more common with placebo-rituximab. All AEs decreased over time. A criticism of the iNNOVATE main study design was the absence of a placebo-ibrutinib arm, not allowing a formal comparison between these treatment options.

Zanubrutinib is a novel oral BTK inhibitor approved by the FDA and EMA for the treatment of adult patients with WM who have received at least one prior therapy, or as first-line treatment in patients for whom chemoimmunotherapy is unsuitable. It is more BTK-specific than ibrutinib.

Zanubrutinib, 160 mg bd, was compared with ibrutinib, 420 g od, in the open-label Phase III ASPEN study.[23] In total, 201 patients with *MYD88* L265P-mutated WM (164 patients with relapsed/refractory disease after one or more prior therapies and 37 treatment-naive patients) were randomized 1:1 to receive open-label zanubrutinib or ibrutinib. At a median follow-up of 19.4 months, no patient had achieved a CR. VGPR attainment, the main outcome, was 28% and 19% (not statistically significant) for zanubrutinib and ibrutinib, respectively. VGPR was 29% versus 20% in relapsed/refractory patients and 26% versus 17% in treatment-naive patients. MRRs were 77% and 78%, and 18-month PFS was 85% and 84% for zanubrutinib and ibrutinib, respectively.

The most common AEs reported among patients who received zanubrutinib were neutropenia, upper respiratory infection and diarrhea. Overall, zanubrutinib was associated with lower rates of AF, hemorrhage, diarrhea, peripheral edema, muscle spasms and pneumonia, higher rates of neutropenia and similar rates of infection compared with ibrutinib (Figure 3.3).

An exploratory substudy of 28 patients (23 with relapsed/refractory disease and 5 previously untreated) without *MYD88* mutation or with unknown mutational status, received zanubrutinib, 160 mg bd. At a median follow-up of 17.9 months, no patient had achieved a CR. VGPR was attained in 27% of patients (7 of 26) with no *MYD88* mutation, and MRR (PR or better) was 50%. The PFS and OS at 18 months were 68% and 88%, respectively. Two patients discontinued treatment because

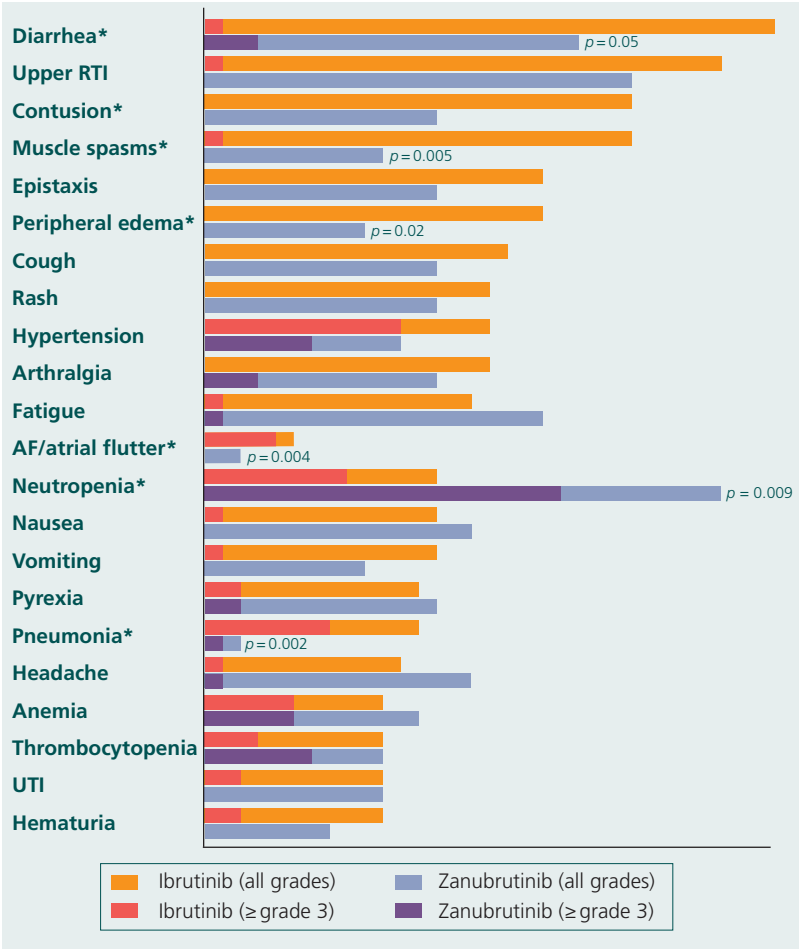

Figure 3.3 Most common AEs (observed in ≥ 10% of patients) after treatment with ibrutinib versus zanubrutinib. *Difference in all-grade incidence is ≥ 10%. Statistical significance is shown for all grades. The differences in incidence between the arms for ≥ grade 3 AF, pneumonia and neutropenia are also statistically significant ($p = 0.02$, 0.02 and 0.03, respectively). Adapted from data in Tam et al. 2020.[23]

of AEs.[24] These results indicate that zanubrutinib may be an effective treatment option for patients with WM who lack an activating *MYD88* mutation. Further study and longer follow-up are needed.

Other covalent BTK inhibitors. Acalabrutinib, 100 mg bd, has been evaluated in 106 patients with WM (14 treatment-naive and 92 previously treated) in a multicenter Phase II study.[25] With a median follow-up of 27 months, the ORR was 93% and MRR was 80%. The 24-month PFS rate was 90% for treatment-naive and 92% for previously treated patients. The MRR in the 14 patients without *MYD88* mutation was 64%. No patient attained VGPR. Grade 3 or higher AEs included neutropenia, infections, thrombocytopenia, anemia and an increase in serum liver enzyme levels. AF occurred in 5% of patients.

Tirabrutinib, 480 mg od, has been studied in 27 patients with WM (18 treatment-naive and 9 relapsed/refractory) in a multicenter Phase II trial, 96.2% of whom had the *MYD88* L265P mutation. MRR and ORR were 88.9% and 96.3%. respectively. Grade 3 or higher AEs included neutropenia, lymphopenia and leukopenia.[26]

BCL2 antagonists

B-cell lymphoma-2 (BCL2) antagonism has shown high efficacy in CLL. Given the expression of BCL2 in WM cells, BCL2 antagonism is of clinical interest in patients with WM. A single-agent Phase II study evaluated the oral BCL2 antagonist venetoclax in 32 previously treated patients with WM, including 16 patients previously exposed to BTK inhibitors (who had a longer time to response: 4.5 vs 1.4 months; $p<0.001$).[27] Venetoclax was administered at doses up to 800 mg daily for up to 2 years in the absence of progression or unacceptable toxicity. ORR, MRR and VGPR were 84%, 81% and 19%, respectively. Median PFS was 30 months. The only recurring AE of grade 3 or higher was neutropenia. One instance of laboratory tumor lysis syndrome (TLS) occurred, but there was no clinical TLS and no deaths. The National Comprehensive Cancer Network (NCCN) endorsed venetoclax for use in patients with previously treated WM.

Maintenance treatment

Maintenance treatment with rituximab is well established in follicular lymphoma, and retrospective data have pointed to a potential

role for rituximab maintenance treatment in patients with WM. In 248 rituximab-naive patients with WM who were either observed or received maintenance rituximab, responses improved in 16 of 162 (10%) observed patients and in 36 of 86 (41.8%) patients who received maintenance rituximab following induction therapy. Both PFS (56.3 vs 28.6 months; $p=0.0001$) and OS (>120 vs 116 months; $p=0.0095$) were longer in patients who received maintenance rituximab.[28]

In a prospective randomized Phase III study, patients with WM were randomized to rituximab maintenance every 8 weeks for 2 years or observation after attaining a PR or better to BR induction therapy. These data, which are still not fully published, did not show any significant difference in PFS (the primary endpoint) between the two groups. As a result, rituximab maintenance is not generally recommended outside of clinical trials in this disease.[29]

High-dose therapy and stem-cell transplantation

Although less frequently used, autologous stem-cell transplantation (SCT) and allogeneic SCT are important treatment options in younger patients with a clinically aggressive course.

In the largest data set from the European Bone Marrow Transplant (EBMT) registry of 158 patients with WM who underwent autologous SCT, 5-year PFS and OS were 39.7% and 68.5%, respectively. Non-relapse mortality at 1 year was 3.8%. Chemorefractory disease and the number of prior lines of therapy at the time of autologous SCT were the most important prognostic factors for both parameters.[30]

EBMT registry data also reported relapse rates at 3 years in 37 and 49 patients who underwent allogeneic SCT with myeloablative or reduced-intensity conditioning regimens, respectively, as 11% and 25%; 5-year PFS and OS were 56% and 62%, and 49% and 64%, respectively. Chronic graft-versus-host disease was associated with improved PFS, indicating a clinically relevant graft-versus-WM effect.[31]

There is consensus that autologous SCT is not appropriate as part of first-line therapy in patients responding to induction therapy, but is a treatment option following second or subsequent relapses in high-risk patients with chemosensitive disease. In addition, allogeneic

SCT should not be considered in patients who have not received BTK inhibitor treatment.

Treatment algorithms

Treatment algorithms have been proposed by national and international treatment guidelines. The algorithms individualize first-line treatment according to fitness, and treatment in relapsed patients according to fitness, duration of response to first-line treatment and the nature of initial treatment (Figure 3.4).

There is a debate as to what extent mutational status of the *MYD88* and *CXCR4* genes should affect treatment choice, with patients who have mutated *MYD88* and wild-type *CXCR4* showing highest sensitivity to ibrutinib. Patients with non-mutated *MYD88* have the lowest response rates to BTK inhibition, although the results from the exploratory cohort in the ASPEN study suggest that zanubrutinib may have potential in these patients (Figure 3.5).

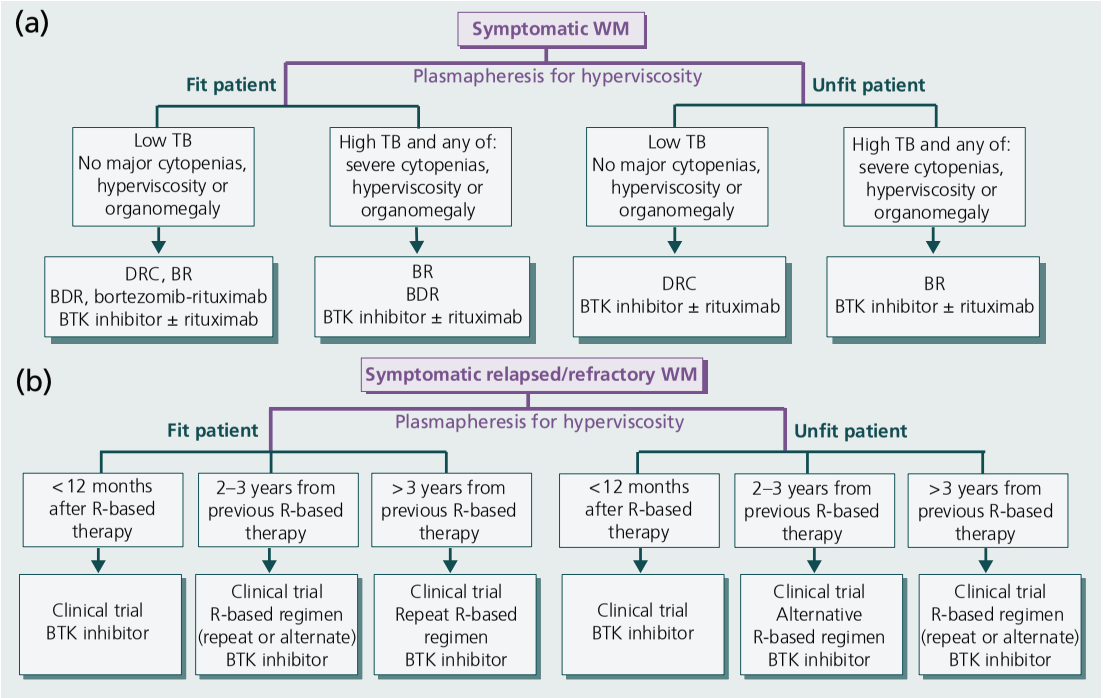

Figure 3.4 Treatment algorithm for (a) newly diagnosed symptomatic patients with WM, and (b) patients with relapsed or refractory WM. R, rituximab; TB, tumor burden. Adapted from Kastritis et al. 2018.[32]

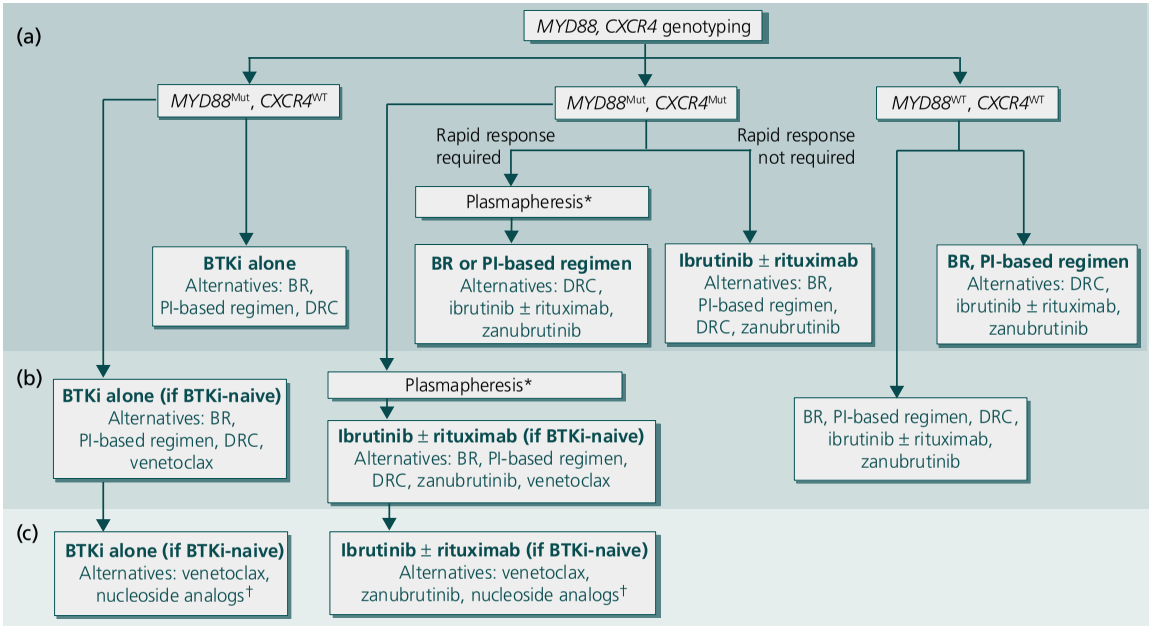

Figure 3.5 Proposed genotype-driven treatment algorithm for symptomatic patients with WM. (a) Primary therapy options for treatment-naive patients. (b) Treatment options after first and second relapse or for refractory patients. (c) Treatment options after third or later relapse or for refractory patients (after alkylator- or proteasome inhibitor [PI]-based regimens). *For severe hyperviscosity, CAD, cryoglobulinemia and/or rapidly progressing IgM peripheral neuropathy. †Should be avoided in younger patients and patients who are eligible for SCT. BTKi, BTK inhibitor; MUT, mutated; WT, wild-type. Adapted from Treon et al. 2020.[33]

Key points – treatment

- Asymptomatic patients are actively monitored until bone marrow infiltration leads to anemia (hemoglobin < 10 g/dL), which the most common reason for starting treatment, a low platelet count ($< 100 \times 10^9$/L), lymphadenopathy compressing vital organs or other symptoms warranting treatment initiation.
- The aim of treatment is to control disease and maintain quality of life. There is no standard treatment. Treatment is personalized according to an individual's disease profile.
- Several agents are used alone or, increasingly, in combination. These include alkylating agents (bendamustine), BTK inhibitors (ibrutinib and zanubrutinib), proteasome inhibitors (bortezomib), monoclonal antibodies (rituximab) and BCL2 inhibitors (venetoclax).
- Rituximab is still a cornerstone of therapy in combination with other agents (BR, DRC and bortezomib–rituximab); however, single-agent rituximab can induce a temporary but potentially significant IgM flare.
- BTK inhibition with ibrutinib (with or without rituximab) or zanubrutinib has changed the treatment landscape of WM.
- Treatment alogrithms have been proposed that individualize first-line treatment according to patient fitness, tumor burden and symptoms, and relapsed treatment according to patient fitness, duration of response to first-line treatment and the nature of initial treatment.
- The patient's *MYD88* and *CXCR4* mutational status may affect treatment choices.
- Autologous and allogeneic SCT are important treatment options for younger patients with aggressive disease after a second or subsequent relapse.

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Oncology
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Hematology

4 Research directions

HEALTHCARE

Despite important advances in the treatment of patients with WM, significant unmet needs still exist and need to be addressed in clinical trials. This is happening, with more clinical trials dedicated to WM than ever before, and the future of treatment for patients with WM looks bright (Table 4.1). With treatment options increasing and new approaches being tested, patients with WM should be encouraged to enroll in clinical trials. This chapter provides an overview of some of the key areas of research being undertaken. Additional areas of active interest include antibody-drug conjugates (ADCs), bispecific T-cell engagers (BiTEs) and chimeric antigen receptor (CAR) T-cell therapy. Large multicenter and preferably randomized studies are needed to move the field forward.

TABLE 4.1

Selected clinical trials evaluating novel agents in WM

ClinicalTrials.gov identifier (Phase)	Agents	Mechanism of action
NCT04263480 (Phase III)	Ibrutinib-carfilzomib vs Ibrutinib	Combination of BTK inhibitor and proteasome inhibitor versus single-agent BTK inhibitor
NCT04061512 (Phase II/III)	Ibrutinib-rituximab vs DCR	Combination of BTK inhibitor and CD20-directed mAb vs chemotherapy
NCT03506373 (Phase II)	Ibrutinib-ixazomib	Combination of BTK inhibitor and proteasome inhibitor
NCT03620903 (Phase II)	Ibrutinib-bortezomib-rituximab	Combination of BTK inhibitor, proteasome inhibitor and CD20-directed mAb
NCT04273139 (Phase II)	Ibrutinib-venetoclax	Combination of BTK inhibitor and BCL2 antagonist

CONTINUED

TABLE 4.1 CONTINUED

Selected clinical trials evaluating novel agents in WM

ClinicalTrials.gov identifier (Phase)	Agents	Mechanism of action
NCT04840602 (Phase II)	Ibrutinib-venetoclax-rituximab vs Ibrutinib-rituximab	Combination of BTK inhibitor, BCL2 antagonist and CD20-directed mAb vs BTK inhibitor and mAb
NCT03679624 (Phase II)	Ibrutinib-daratumumab	Combination of BTK inhibitor and CD38-directed mAb
NCT03630042 (Phase II)	Pembrolizumab-rituximab	Combination of PD-1-directed immune checkpoint inhibitor and CD20-directed mAb
NCT04624906 (Phase II)	Bendamustine-rituximab-acalabrutinib	Combination of chemo-immunotherapy and BTK inhibitor
NCT03364231 (Phase II)	Umbralisib	PI3K inhibitor
NCT03162536 (Phase I/II)	ARQ-531	Non-covalent BTK inhibitor
NCT03740529 (Phase I/II)	Pirtobrutinib	Non-covalent BTK inhibitor
NCT03225716 (Phase I/II)	Ibrutinib-ulocuplumab	Combination of BTK inhibitor and CXCR4-directed mAb
NCT04274738 (Phase I/II)	Ibrutinib-mavorixafor	Combination of BTK inhibitor and CXCR4 antagonist
NCT02952508 (Phase I/II)	CLR-131	Phospholipid-drug conjugate

mAb, monoclonal antibody; PD-1, programmed cell death 1; PI3K, phosphatidylinositol-3 kinase.

BTK inhibitors or immunochemotherapy?

At present, it is unclear if BTK inhibitor-based regimens are superior to chemoimmunotherapy regimens. Head-to-head trials are needed to address this. A British Phase II/III randomized study is aiming to enroll 148 treatment-naive patients with WM to compare ibrutinib-rituximab versus DCR (NCT04061512; RAINBOW). The primary outcomes of this study are ORR at 24 weeks and PFS 2 years after the last randomization. In addition, the European Consortium for Waldenström's Macroglobulinemia (ECWM) is initiating a randomized trial comparing DRC with timely fixed-duration treatment with venetoclax-rituximab.

Improving the CR rate

An important unmet need in patients with WM is the low rates of CR attained with current standard therapies. At best, the CR rates are less than 10%.[1–3] In other lymphoproliferative malignancies, such as multiple myeloma or CLL, the concept of minimal residual disease (MRD) has been introduced.[4,5] In these conditions, however, the rates of CR range between 30% and 50%. MRD refers to the detection of residual malignant disease when so few cancer cells are present that they cannot be identified by routine means. These patients would meet the standard criteria for CR, but flow cytometry or genomic testing can detect malignant cells with a 10^{-4} to 10^{-5} sensitivity. Importantly, MRD has been associated with worse outcomes in patients who attain a CR. In WM, it would be difficult to consider assessing for MRD without attaining higher rates of CR first.

To address this unmet need, clinical trials are needed that evaluate combinations of agents with distinct mechanisms of action.

Proteasome inhibitor plus immunochemotherapy. A multicenter European randomized Phase II study is evaluating 6-monthly cycles of bortezomib-DRC (B-DRC) versus DRC.[6] At a median follow-up of 27.5 months, the CR/VGPR rate of B-DRC was 19% versus 11% for DRC, with a 24-month PFS of 81% versus 73%. Both regimens were well tolerated, with low rates of neuropathy in the B-DRC arm. Longer follow-up is needed to understand the PFS benefit of adding a proteasome inhibitor to combination chemoimmunotherapy.

BTK inhibitor plus proteasome inhibitor. Concurrent inhibition of the BTK and proteasome pathways has shown synergistic WM-cell killing in preclinical studies. Several clinical trials are evaluating the combination of ibrutinib and proteasome inhibitors in patients with WM. An open-label Phase III study to evaluate ibrutinib with and without carfilzomib is currently recruiting, with the aim of enrolling 184 treatment-naive and previously treated patients with WM (NCT04263480; CZAR-1). Ibrutinib will be given daily until disease progression or unacceptable toxicity. Carfilzomib will be given in 28-day cycles, on days 1, 8 and 15 on cycles 1–12, and on days 1 and 15 on cycles 13–24. The primary outcome is the rate of CR/VGPR at 12 months after start of treatment.

The combination of ibrutinib-bortezomib-rituximab is being evaluated in a Phase II study, which aims to enrol 53 previously untreated patients with WM (NCT03620903). The study design includes 6 induction cycles of ibrutinib-bortezomib-rituximab followed by two types of maintenance. In one arm, the patients will receive ibrutinib indefinitely (for a maximum of 10 years) plus rituximab every 2 months for 24 months. In the other, the patients will receive ibrutinib indefinitely (for a maximum of 10 years). The primary outcome is the rate of CR/VGPR at 12 months after start of treatment.

A Phase II study is evaluating the combination of ibrutinib-ixazomib in 47 previously treated patients with WM (NCT03506373). Ibrutinib daily and ixazomib on days 1, 8 and 15 will be administered in 28-day cycles for up to 24 cycles in the absence of disease progression or unacceptable toxicity. The primary outcome is the rate of CR at any time after start of treatment.

BTK inhibitor plus BCL2 antagonist. Given the encouraging results of single-agent venetoclax (see page 50), a Phase II study is evaluating ibrutinib-venetoclax in 50 treatment-naive patients with WM (NCT04273139). Ibrutinib and venetoclax will be administered daily in 28-day cycles for up to 24 cycles in the absence of progression or unacceptable toxicity. The primary outcome is the rate of CR/VGPR at any time after start of treatment.

A randomized Phase II study is also recruiting patients to evaluate ibrutinib-rituximab with and without venetoclax (NCT04840602).

In both arms, combination therapy will be given for 24 cycles every 28 days. The primary outcome is the rate of CR at any time after start of treatment.

Meanwhile, a Phase I study will be evaluating the novel BCL2 antagonist ACP-2575 alone or in combination with ibrutinib or rituximab (NCT04260217).

PI3K inhibitors

The phosphatidylinositol-3 kinase (PI3K) pathway plays an important role in B-cell receptor signaling, and its blockade has been shown to induce WM-cell killing in preclinical models.[7] The PI3K inhibitor idelalisib has shown initial activity in patients with indolent non-Hodgkin lymphoma in a Phase I/II clinical trial that included patients with WM.[8] However, a Phase II study that aimed to recruit 30 patients with previously treated WM was stopped early after enrolling just 5 patients because of high rates of liver toxicity.[9] A French study evaluated the combination of idelalisib-obinutuzumab in 48 patients with previously treated WM.[10] ORR and MRR were 71% and 65%, respectively, with a median PFS of 25 months. However, more than 50% of the patients discontinued treatment because of AEs, which included neutropenia, diarrhea and liver toxicity. A Phase II study is currently evaluating the novel PI3K inhibitor umbralisib in patients with WM (NCT03364231).

Monoclonal antibodies

Daratumumab has been shown to be active in patients with myeloma and systemic AL amyloidosis.[11,12] In a Phase II study that enrolled 13 of 30 planned previously treated patients with WM, the anti-CD38 monoclonal antibody daratumumab produced an ORR of 23%, prompting early termination of the study.[13] Preclinical studies, however, have suggested a synergistic killing effect of daratumumab and ibrutinib in WM cells.[14] A Phase II two-cohort study is therefore evaluating ibrutinib-daratumumab in patients with WM (NCT03679624). Cohort A, comprising ibrutinib-naive patients, will start with ibrutinib-daratumumab; cohort B patients will start with ibrutinib, and daratumumab will be added after a response plateau has been attained.

Immune checkpoint inhibitors

Pembrolizumab is a programmed cell death protein 1 (PD-1) monoclonal antibody used to treat Hodgkin lymphoma and other malignancies.[15,16] High levels of soluble PD-1 ligands, which have the potential to promote disease progression by regulating T-cell function, have been detected in the serum of patients with WM.[17] A Phase II study is recruiting patients to evaluate pembrolizumab-rituximab in previously treated patients with WM (NCT03630042). The study aims to enroll 42 patients, and the primary outcome is the rate of PR or better at 24 weeks after treatment initiation.

Managing resistance to BTK inhibitors

Covalent BTK inhibitors have become a standard of care for the treatment of patients with WM. However, the *BTK* C481S mutation in WM-cell clones has been associated with resistance to these agents.[18] It is unclear what the most effective treatment options are for patients with WM who progress on standard BTK inhibitors. If the patient has not been previously exposed to an alkylator or proteasome inhibitor-based regimen, these are reasonable treatment options.[19] However, for patients who have been previously exposed to these agents, and whose disease is progressing while receiving a BTK inhibitor, effective treatment options are limited. It is important to note that 50% of patients with WM experience an IgM rebound within 4 weeks and 80% within 8 weeks of stopping ibrutinib.[20] The IgM rebound off ibrutinib can be symptomatic and hard to control without effective subsequent therapies.

Non-covalent BTK inhibitors exert their inhibitory function without interacting with the 481 loci in BTK and therefore could be effective in patients with WM progressing on covalent BTK inhibitors. A Phase I/II study evaluated the non-covalent BTK inhibitor pirtobrutinib in patients with previously treated indolent B-cell lymphomas, including WM.[21] Doses were escalated from 25 mg to 300 mg od, with a recommended Phase II dose of 200 mg od. Of 19 patients with WM, 8 had progressed on, and 6 were intolerant to, a covalent BTK inhibitor, and 5 were BTK-inhibitor naive. ORR was 68%, including patients (47%) attaining a PR to pirtobrutinib. A dedicated study in patients with WM is being planned.

The oral non-covalent BTK inhibitor ARQ-531 is also being evaluated in a Phase I/II study of patients with previously treated B-cell malignancies, including WM (NCT03162536). Preliminary results were presented at the 2019 annual meeting of the American Society of Hematology but did not include data on patients with WM.[22]

CXCR4 antagonists. Approximately 40% of patients with WM harbor mutations in *CXCR4*, which confer resistance to BTK inhibitors and are characterized by lower rates of VGPR and shorter PFS.[23,24] Mutated *CXCR4* provides a supplemental activation pathway to malignant WM cells that is not completely abrogated by BTK inhibition.[25] The CXCR4 pathway is therefore an important therapeutic target. Ulocuplumab and mavorixafor are CXCR4-targeting agents in clinical development for patients with WM who have *CXCR4* mutations. Ulocuplumab is a humanized CXCR4-directed monoclonal antibody, and mavorixafor is a small-molecule CXCR4 inhibitor.

A Phase I study is evaluating ibrutinib-ulocuplumab (NCT03225716) in 13 patients with WM. Ulocuplumab was administered intravenously for the first 6 months of the study and ibrutinib is being given until disease progression or unacceptable toxicity. The main outcome of the study is to determine the maximum tolerated dose of ulocuplumab.

Ibrutinib-mavorixafor is being evaluated in patients with WM who have *CXCR4* mutations in a multicenter Phase Ib study (NCT04274738). The study aims to enrol 18 patients, and both agents will be administered until disease progression or unacceptable toxicity.

Other small molecules. CLR-131 is a small-molecule phospholipid-drug conjugate that delivers a radioisotope to cancer cells. The FDA has granted CLR-131 fast track and orphan drug designations for relapsed or refractory WM, myeloma and DLBCL. A Phase II study (NCT02952508) is looking to enroll 120 patients to evaluate the safety and efficacy of CLR-131 in patients with B-cell malignancies (CLOVER-1) with an expansion in patients with WM who have failed first-line therapy and have failed to respond to, or have progressed on, a BTK inhibitor (CLOVER-WaM).

Immunotherapy. Novel immunotherapeutic agents such as ADCs, BiTEs and CAR T cells have been recently approved or are undergoing clinical development for the treatment of patients with B-cell malignancies and multiple myeloma.[26–29] These approaches are expected to expand into, and be effective in, rarer B-cell lymphomas such as WM, as most of these agents target B-cell or plasma-cell markers such as CD19, CD20, BCMA and CD79, which are expressed in WM cells. Despite the exciting possibilities, careful clinical trial designs for patients with WM are warranted to identify and manage toxicities that are inherent to these treatments, such as cytokine release syndrome, or toxicities that are potentially unique to patients with WM, such as serum IgM flare.

Key points – research directions

- Despite many important therapeutic advances, there are still considerable unmet needs in the treatment of patients with WM that need to be explored in future clinical trials. Patients with WM should be encouraged to enroll in trials exploring new therapeutic options.
- Current standard therapies produce only low rates of CR, at best less than 10%. New trials are needed to evaluate different combination regimens, particularly therapies with different mechanisms of action, with the aim of raising the level of CR for patients with WM.
- *CXCR4* mutations are found in approximately 40% of patients with WM and the CXCR4 pathway is therefore an important therapeutic target.
- Combination therapies under investigation include bortezomib-DRC, ibrutinib-carfilzomib, ibrutinib-bortezomib-rituximab, ibrutinib-venetoclax and ibrutinib-venetoclax-rituximab.
- Additional areas of interest include ADCs, BiTEs and CAR T-cell therapy.
- Current research activity bodes well for future WM treatment.

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Useful resources

Amyloidosis Foundation (USA)
amyloidosis.org

European Consortium for Waldenström's Macroglobulinemia
ecwm.eu

International Waldenström's Macroglobulinemia Foundation
iwmf.com

Lymphoma Action (UK)
lymphoma-action.org.uk

WMUK
wmuk.org.uk

Waldenström's Macroglobulinemia Foundation of Canada
wmfc.ca

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