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CLINICAL PRACTICE GUIDELINES

Waldenström's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Incidence and epidemiology

Waldenström's macroglobulinaemia (WM) is a rare disease that accounts for 1%–2% of non-Hodgkin lymphomas. The reported age-adjusted incidence rate is 3.4 per million among the male population and 1.7 per million among the female population in the United States, and 7.3 and 4.2 per million, respectively, in the European standard population [1, 2]. In contrast to multiple myeloma, WM prevalence is higher among Caucasians than among African-Americans (IRR: 1.75) [3]. WM is a disease of the elderly, with the median age at the time of diagnosis being 63–75 years in different series [3–5]. A strong familial predisposition has been reported [6–8] and first degree relatives of WM patients have up to 20-fold increased risk for developing WM (and also increased risk but at lower level for other B-cell disorders) [9].

Diagnosis

The diagnosis of WM is based on the histopathological confirmation of bone marrow (BM) infiltration by lymphoplasmacytic cells/lymphoplasmacytic lymphoma (LPL) and the detection of any amount of monoclonal immunoglobulin M (IgM) protein [10, 11], which should always be confirmed by immunofixation. The presence of monoclonal IgM without the histopathological diagnosis of LPL in the BM is not considered as WM, because this situation could correspond to monoclonal gammopathy of undetermined significance (MGUS), or to a nodal LPL without BM infiltration. A diagnosis of LPL without detection of monoclonal IgM does not fulfil the criteria for WM. The clonal lymphoplasmacytic cell population in the BM (which contains a population with lymphocytic differentiation and one with plasmacytic differentiation) should be documented by a trephine biopsy and/or aspiration and confirmed by immunophenotypic studies (immunohistochemistry or flow cytometry) showing expression of CD19, CD20, CD22 and CD79a on the lymphocytic as well as CD38 on the plasmacytic component (small variations can occur) [10, 11]. Multiparametric flow cytometry may provide additional data on the immunophenotypic characterisation of WM showing accumulation of light-chain-isotype-positive B cells with a characteristic phenotype [CD22(+dim)/CD25+/CD27+/IgM+] that differs from other B-lymphomas by negative expression of CD5, CD10, CD11c or CD103 [12].

About 90% of patients with WM harbour the myeloid differentiation primary response $MYD88^{L265P}$ gene mutation in their lymphoplasmacytic cells [13], which can be helpful for the differential diagnosis from other morphologically similar diseases (such as multiple myeloma). The $MYD88^{L265P}$ mutation alone is not diagnostic of WM. This mutation is also found in 50%–80% of patients with IgM MGUS and may also be found in other lymphomas such as marginal zone lymphoma. Furthermore, 5%–10% of patients who fulfil the immunophenotypic and clinical criteria of WM do not have the $MYD88^{L265P}$ mutation (they may either have other *MYD88* mutations [14] or may have wild type *MYD88*). Diagnostics for the detection of $MYD88^{L265P}$ have not been standardised but should be based on BM sampling, because

Table 1. Diagnostic work-up

Recommended

- History and physical examination
  - Include familial history for WM and other B cell lymphoproliferative disorders
- Review of systems (B symptoms[a], organomegaly, hyperviscosity symptoms, neuropathy, Raynaud's disease, rash, peripheral oedema, skin abnormalities, dyspnoea)
  - Include fundoscopic examination if IgM is high and hyperviscosity is suspected
- Laboratory studies:
  - Complete blood count
  - Complete metabolic panel
  - Serum Ig levels (IgA, IgG, IgM)
  - Serum and urine electrophoresis with immunofixation
  - Serum B2M level
  - Viral serology (HBV, HCV and HIV)
- BM aspiration and biopsy
  - IHC (required for diagnosis)
  - Flow cytometry (optional; consider if IHC not available)
  - Testing for *MYD88*^{L265P} gene mutation
- CT of the chest, abdomen and pelvis (if clinically indicated and in all patients being considered for therapy)

Optional (if clinically indicated)

- Cryoglobulins
- Cold agglutinin titre
- Serum viscosity
- Screening for acquired von Willebrand disease
- 24-h urine protein quantification
- Serum FLCs
- NTproBNP, cardiac troponins
- EMG, anti-MAG, anti-GM1 (consultation with neurologist)

[a]Fever, night sweats and weight loss.

anti-GM1, anti-ganglioside M1; anti-MAG, myelin-associated globulin antibody; B2M, β2 microglobulin; BM, bone marrow; CT, computed tomography; EMG, electromyogram; FLC, free light chain; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IHC, immunohistochemistry; Ig, immunoglobulin; NTproBNP, N-terminal pro b-type natriuretic peptide; WM, Waldenström's macroglobulinaemia.

Table 2. Prognostification of WM (IPSSWM) (adapted from [19])

Risk group	Stage 1 (low risk)	Stage 2 (intermediate risk)	Stage 3 (high risk)
Risk factors present[a]	0 or 1 (except age)	Age or 2	≥ 3
5-year OS (%)	87	68	36

[a]Risk factors for IPSSWM include: age ≥ 65 years, Hb ≤ 11.5 g/dL, platelets ≤ 100×10^9/L, B2M > 3 mg/L and IgM > 70 g/L. Other risk factors not included in IPSSWM include elevated serum LDH and low serum albumin.

B2M, β2 microglobulin; Hb, haemoglobin; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström's macroglobulinaemia; LDH, lactate dehydrogenase; OS, overall survival; WM, Waldenström's macroglobulinaemia.

Table 3. Indications for initiation of therapy in patients with WM [31]

Clinical indications for initiation of therapy

Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy: either symptomatic or bulky (≥ 5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy due to WM

Laboratory indications for initiation of therapy

Symptomatic cryoglobulinaemia
Symptomatic cold agglutinin anaemia
Autoimmune haemolytic anaemia and/or thrombocytopaenia
Nephropathy-related to WM
Amyloidosis-related to WM
Hb ≤ 10 g/dL
Platelets < 100×10^9/L
IgM levels > 60 g/L

Hb, haemoglobin; IgM, immunoglobulin M; WM, Waldenström's macroglobulinaemia.

peripheral blood detection may give false-negative results [15]. A sensitive method, such as allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) is recommended and each laboratory should report the method and detection limits. The use of molecular methods for *MYD88*^{L265P} detection and flow cytometry may also be useful for the diagnosis of cases with extranodal involvement (pleura, central nervous system, etc.) [16]. Activating C–X–C chemokine receptor type 4 (*CXCR4*) mutations are found in ∼30% of patients with WM [13]. More than 30 different *CXCR4* mutations have been described in WM, complicating diagnostic standardisation. Since there are as yet no therapeutic implications outside clinical trials, diagnostic testing for the presence or the absence of *CXCR4* mutations is not routinely recommended. However, in patients considered for treatment with ibrutinib, *CXCR4* mutational status may be evaluated given the effects in depth and response kinetics in those with *CXCR4* mutations [17, 18].

Staging and risk assessment

Besides patient history and documentation of symptoms, initial evaluation should include a complete blood count (CBC) with differential and serum chemistry, including lactate dehydrogenase (LDH) and serum albumin. Anaemia may be the only indication for therapy, and thus its association with WM and not to other concomitant disorders should be confirmed [e.g. by evaluation of iron status (ferritin) or additional tests]. The β2 microglobulin (B2M) level should be measured: it is a prognostic marker for survival and a component of the International Prognostic Scoring System for WM (IPSSWM) [19]. Serum protein electrophoresis and immunofixation and quantification of Ig levels (IgM, IgG, IgA) are essential at initial assessment. The determination of IgM levels can be based either on densitometry or

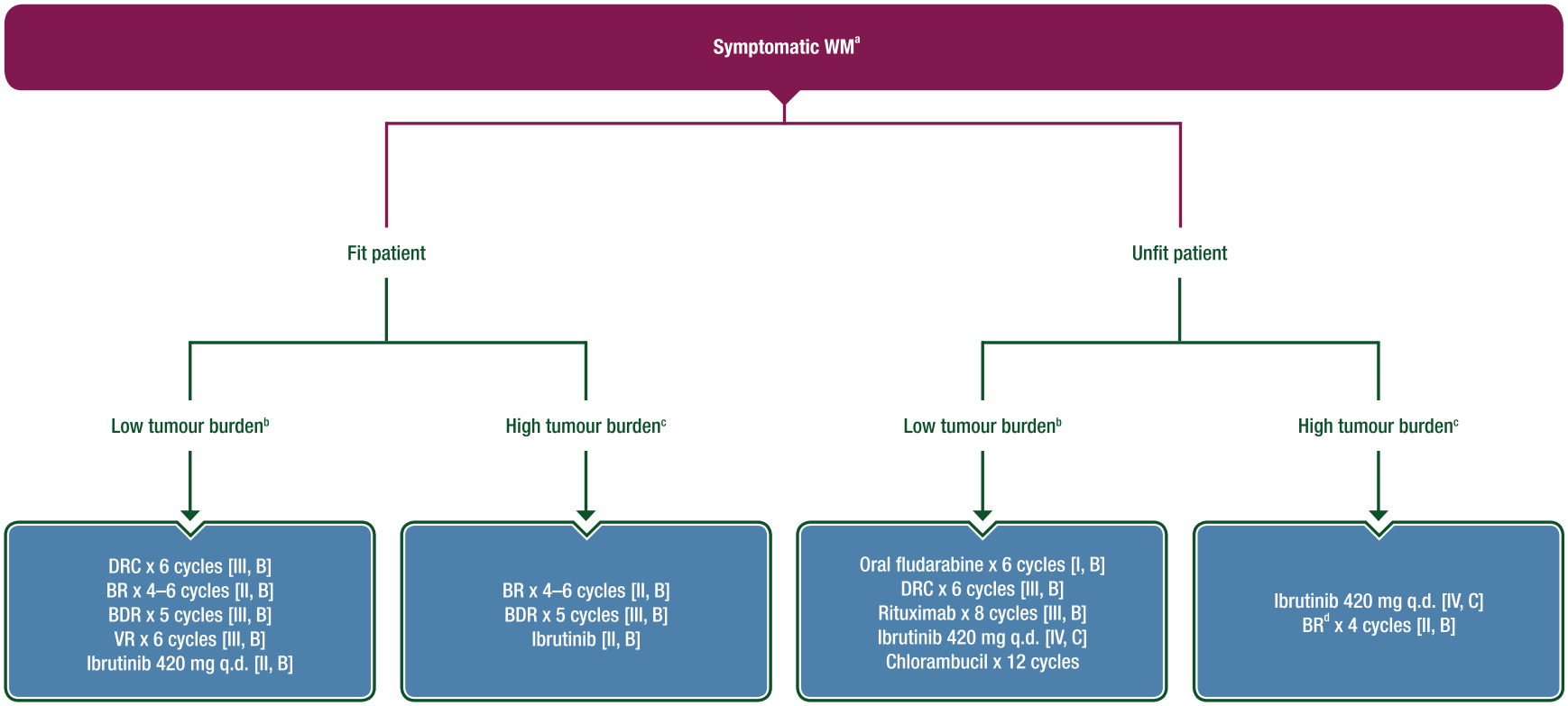

Figure 1. Treatment algorithm for patients with newly diagnosed WM.
[a]In case of hyperviscosity, plasmapheresis should be used concomitantly with systemic therapy [IV, A]. In case of high IgM levels and at risk for IgM-related complications, plasmapheresis may be used pre-emptively [IV, A].
[b]No major cytopaenias, hyperviscosity or organomegaly.
[c]Presence of any of the following: severe cytopaenias, hyperviscosity, organomegaly.
[d]BR for unfit patients may require dose reductions for bendamustine and use of G-CSF and/or antibacterial/antiviral prophylaxis.
BDR, bortezomib/rituximab/dexamethasone; BR, bendamustine/rituximab; DRC, rituximab/cyclophosphamide/dexamethasone; G-CSF, granulocyte colony-stimulating factor; IgM, immunoglobulin M; q.d., once a day; VR, bortezomib/rituximab; WM, Waldenström's macroglobulinaemia.

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Table 4. Treatment options in first line according to disease presentation

Clinical syndrome	Treatment options
Hyperviscosity	PI-based therapy (BDR, VR) Ibrutinib BR
Cytopaenias	DRC PI-based therapy (BDR, VR) BR Ibrutinib
Bulky disease	BR PI-based therapy (BDR, VR) Ibrutinib
Need for immediate tumour reduction (due to WM-related complications)	PI-based therapy (BDR, VR) BR Ibrutinib
Neuropathy	DRC BR Rituximab monotherapy
AL amyloidosis	PI-based therapy (BDR, VR) BR

AL, amyloid light chain; BDR, bortezomib/dexamethasone/rituximab; BR, bendamustine/rituximab; DRC, dexamethasone/rituximab/cyclophosphamide; PI, proteasome inhibitor; VR, bortezomib/rituximab; WM, Waldenström's macroglobulinaemia.

on total serum IgM quantification by nephelometry, although densitometry may be more accurate [20]. For response assessments, the same method should be used for the sequential measurement of IgM for an individual patient, ideally in the same laboratory as intra-laboratory and inter-laboratory variation can occur as well [21, 22]. The usefulness of measurement of serum free light chain (FLC) in patients with WM is still under investigation and is recommended in situations where there is suspicion of light chain (AL) amyloidosis or renal failure, or in the rare occasion of a patient with measurable FLCs levels but very low (and non-quantifiable) IgM levels. However, in patients with renal failure the evaluation of FLCs may be challenging [23]. Urine protein electrophoresis and/or urine immunofixation for exclusion of abnormal renal Ig secretion should be carried out (Table 1).

Hyperviscosity syndrome related to high IgM levels is common in WM. Serum viscosity measurement may be considered in patients with symptoms of hyperviscosity (headaches, blurry vision or visual loss, confusion, epistaxis) but does not correlate well with the clinical severity of the syndrome. Fundoscopic examination showing venous engorgement (sausaging) of the retinal veins is a more reliable sign of clinically relevant hyperviscosity [24]; a baseline photography of the retina may help for future comparisons. However, the interpretation of fundoscopic signs should also take into account associated comorbidities such as arterial hypertension or diabetes that may cause or contribute to the observed abnormalities. Testing for cold agglutinins and cryoglobulins should be carried out at diagnosis in patients with symptoms or laboratory evidence suggestive of their presence; physicians should be aware that the presence of cold agglutinins or cryoglobulins may affect the determination of IgM levels. Coombs testing and cold agglutinin titres are indicated if anaemia with evidence of haemolysis occurs. In patients with Raynaud-like symptoms, acrocyanosis, ulcerations of the extremities or hyperviscosity testing for cryoglobulins should be considered. In case of bleeding, diathesis screening for acquired von Willebrand disease should be carried out (Table 1). Viral serology for hepatitis B and C viruses (HBV and HCV) and human immunodeficiency virus (HIV) is strongly recommended, especially before therapy initiation.

Neuropathy is common in patients with WM and often an indication for treatment of otherwise asymptomatic patients; however, other unrelated causes for neuropathy may also exist. The most common clinical presentation is a slowly progressing, demyelinating, symmetrical sensory peripheral neuropathy, usually affecting initially the feet [25]. Myelin-associated globulin antibodies (anti-MAGs) are detectable in the serum of ~50% of these patients and should be evaluated [26]. Anti-ganglioside M1 (GM1) antibodies may also be evaluated if motor neuropathy predominates [27]. Axonal degeneration may be found in patients with longstanding sensorimotor neuropathy or amyloidosis. Small fibre neuropathy can also be seen. In patients with peripheral neuropathy, consultation with a neurologist and specialised neurological evaluation including electromyography/nerve conduction studies should be considered [25]. Nerve biopsies are generally not indicated.

Amyloidosis is an infrequent complication of WM mostly affecting kidneys, heart, liver and peripheral nerves [28, 29]. AL amyloidosis is the most common type in WM, but other types such as amyloid A (AA) amyloidosis have been described. If suspected, a fat aspirate and evaluation of the BM biopsy with Congo red can help establish the diagnosis. Organ assessment with cardiac imaging [echocardiography (echo), cardiac magnetic resonance (CMR)] and cardiac biomarkers [N-terminal pro b-type natriuretic peptide (NTproBNP), troponins], renal markers [24-hour proteinuria, estimated glomerular filtration rate (eGFR)] and liver function tests should be carried out.

At diagnosis, imaging studies should be included in the evaluation to document organomegaly and/or lymphadenopathy, preferably with computed tomography (CT) or magnetic resonance imaging (MRI). Positron emission tomography (PET) scanning does not seem to offer additional information [30] unless transformation to an aggressive lymphoma or another malignancy is suspected, in which case a biopsy of the most fluorodeoxyglucose (FDG)-avid target lesion is indicated.

Risk assessment is currently based on the IPSSWM (Table 2) [19]; however, this prognostic tool was designed only for symptomatic patients.

Management

Asymptomatic patients

Table 3 depicts indications to start therapy. Patients with asymptomatic disease should be followed without therapy [III, C] [31–33]. The median time to symptom development for patients

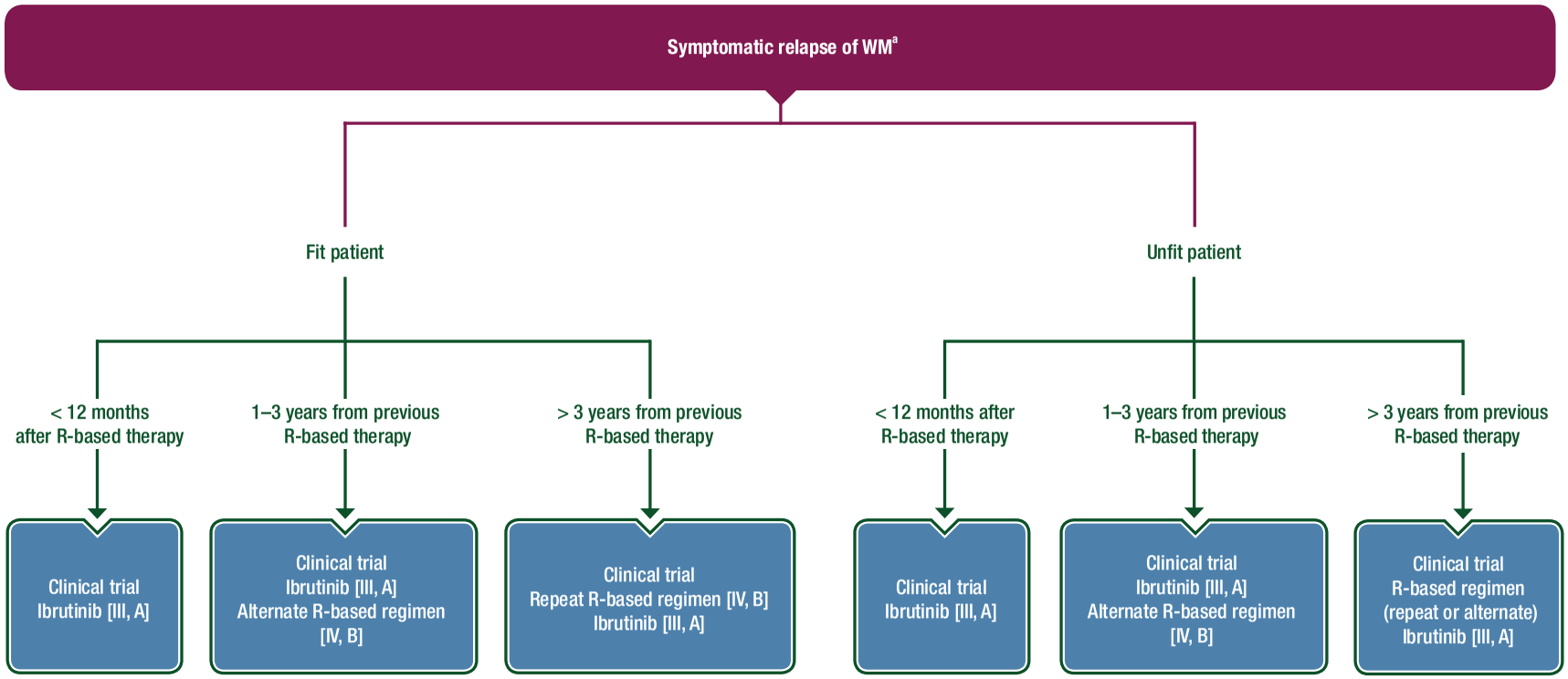

Figure 2. Treatment algorithm for patients with relapsed or refractory WM.
[a]In case of hyperviscosity, plasmapheresis should be used concomitantly with systemic therapy [IV, A]. In case of high IgM levels and at risk for IgM-related complications, plasmapheresis may be used pre-emptively [IV, A].
IgM, immunoglobulin M; R, rituximab; WM, Waldenström's macroglobulinaemia.

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Table 5. Response categories and criteria [21]

Response category	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level[a] Complete resolution of lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Detectable monoclonal IgM protein ≥ 90% reduction in serum IgM level from baseline[b] Complete resolution of extramedullary disease, i.e. lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Detectable monoclonal IgM protein ≥ 50% but < 90% reduction in serum IgM level from baseline[b] Reduction in extramedullary disease, i.e. lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Detectable monoclonal IgM protein ≥ 25% but < 50% reduction in serum IgM level from baseline[b] No new signs or symptoms of active disease
Stable disease (SD)	Detectable monoclonal IgM protein < 25% reduction and < 25% increase in serum IgM level from baseline[b] No progression in extramedullary disease, i.e. lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥ 25% increase in serum IgM level[a,b] from lowest nadir and/or Progression in clinical features attributable to the disease

[a]IgM responses/progression should be confirmed by a second measurement.
[b]Sequential changes in IgM levels may be determined either by IgM protein quantification by densitometry or total serum IgM quantification by nephelometry.
IgM, immunoglobulin M.

with asymptomatic WM exceeds 5–10 years. Patients with low haemoglobin levels, high lymphoplasmacytic cell infiltration and IgM-spike and high B2M level may be at higher risk for development of symptomatic WM [34, 35]. No data exist to support early initiation of therapy over a watch and wait strategy. The level of monoclonal IgM alone is not considered an indication to start treatment [III, C] [31–33]. However, a recent study indicated that IgM levels > 60 g/L are associated with imminent risk of symptomatic hyperviscosity and are therefore considered to be a treatment indication [36]. The most common indications for treatment initiation include anaemia, B symptoms and hyperviscosity; other indications such as neuropathy, bulky organomegaly and immune related cytopaenias are less common.

First-line therapy (Figure 1)

Participation in clinical trials is strongly encouraged for all patients, given the increasing treatment options and promising new approaches. Treatment choice is guided by the clinical presentation of the disease (i.e. mainly cytopaenias versus hyperviscosity) or complications requiring immediate treatment response versus immunological complications without high BM infiltration or presentation with bulky disease (such as massive orgamomegaly/lymphadenopathy, hyperviscosity) (Table 4 and Figure 1). For the immediate relief of symptomatic hyperviscosity, plasmapheresis should be used concomitantly with the appropriate systemic therapy [IV, A] [33, 37].

Anti-CD20-based (rituximab-based) combinations are the mainstay of first-line treatment. A transient increase of serum IgM (IgM flare) occurs in 30%–80% of patients treated with rituximab-based therapies, which may exacerbate IgM-related complications [38, 39]. Pre-emptive use of plasmapheresis may be considered in symptomatic patients with very high levels of IgM and at high risk for hyperviscosity or IgM-related complications before starting anti-CD20-based chemoimmunotherapy [V, B]. Combinations of rituximab with oral or intravenous (i.v.) cyclophosphamide and dexamethasone (DRC regimen for six cycles) induce higher response rates than rituximab alone, but complete responses (CRs) are infrequent. DRC is associated with a progression-free survival (PFS) of about 3 years, a treatment-free interval > 4 years and median overall survival (OS) of ∼8 years with favourable short- and long-term safety profiles [40]. DRC or similar regimens are primary options for patients with low tumour burden and comorbidities [III, B].

Bendamustine with rituximab (BR for four to six cycles) is associated with longer PFS and OS than rituximab with cyclophosphamide/doxorubicin/vincristine/prednisolone (R-CHOP), based on a sub-analysis of a randomised study [41]. Dose intensity of bendamustine should be adapted to the individual characteristics of the patients by reducing the number of cycles and/or by reducing the dosing per cycle. BR has not been prospectively compared with DRC but is a primary option for patients with high tumour burden [II, B]; no data are available to support the role of BR in patients with hyperviscosity.

Bortezomib alone or in combination with rituximab (VR) is very active in WM [42–44] and should preferably be given subcutaneously (s.c.) and at weekly intervals (1.6 mg/m^2). Long-term follow-up of a phase II study of bortezomib/dexamethasone/rituximab (BDR for five cycles) has shown a median PFS of 3.5 years, median duration of major response of 5.5 years and OS rate of 66% at 7 years [42]. The addition of dexamethasone to bortezomib may be beneficial [45]; the use of dexamethasone in bortezomib/rituximab combinations has not been addressed but the choice between VR or BDR should be individualised according to the patient's characteristics (i.e comorbidities such as diabetes etc.). Neurotoxicity is the main concern with bortezomib. The non-neurotoxic proteasome inhibitor carfilzomib has been tested in a small trial, but this agent may also be associated with

Table 6. Summary of recommendations

Diagnosis

- A diagnosis of WM requires histopathological confirmation of BM infiltration by monoclonal lymphoplasmacytic cells and serum monoclonal IgM of any amount, confirmed by immunofixation
- WM cells are typically positive for CD19, CD20, CD22 and CD79a
- About 90% of WM cases are positive for the *MYD88*^{L265P} mutation, which can be helpful for discriminating WM from other lymphoma subtypes and IgM multiple myeloma

Staging and risk assessment

- Initial evaluation includes a CBC, serum chemistry, B2M, serum protein electrophoresis and IgM quantification
- In patients with symptoms of hyperviscosity, fundoscopic examination is recommended
- Coombs testing, cold agglutinins, cryoglobulins and iron status should be considered in patients with anaemia
- Neuropathy is common; consultation of a neurologist is strongly recommended since neuropathy may not always be WM-associated
- Amyloidosis is an uncommon complication in WM and, if suspected, a fat aspirate stained with Congo red and cardiac and renal biomarkers should be evaluated
- Imaging studies should be included in the initial evaluation (preferably CT or MRI)
- Risk assessment is currently based on the IPSSWM

Management

- Asymptomatic patients should not be treated but followed every 3–6 months [III, C]
- In general, the level of monoclonal IgM alone is not an indication to start treatment [III, D]
- Plasmapheresis should be used for the immediate relief of hyperviscosity syndrome along with appropriate systemic therapy [IV, A]
- Indications for therapy include the presence of B symptoms[a], cytopaenias, hyperviscosity, moderate or severe neuropathy, amyloidosis, symptomatic cryoglobulinaemia or cold agglutinin disease
- Combinations of rituximab with alkylating agents (oral or i.v. cyclophosphamide or bendamustine) or with proteasome inhibitors are primary treatment options
- Single-agent therapy with alkylating agents or nucleoside analogues or rituximab is only considered for patients unfit for more effective chemoimmunotherapy combinations
- Maintenance treatment with rituximab is not recommended for patients with WM [IV, C]
- For patients who have relapsed within 12 months from chemoimmunotherapy, including rituximab-refractory patients, single-agent ibrutinib is the treatment of choice [III, A]
- For patients ineligible for chemoimmunotherapy at first-line, single agent ibrutinib may be considered [V, B]
- For patients with late relapses after chemoimmunotherapy, an alternate chemoimmunotherapy combination or a prior effective regimen or ibrutinib [III, A] may be considered
- High-dose therapy with ASCT may be considered in selected young patients with chemosensitive relapse [IV, B]
- Participation in clinical trials is strongly encouraged for all patients, either in first line or subsequent lines of therapy

[a]Fever, night sweats and weight loss.

ASCT, autologous stem-cell transplantation; B2M, β2 microglobulin; BM, bone marrow; CBC, complete blood count; CT, computed tomography; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström's macroglobulinaemia; i.v. intravenous; MRI, magnetic resonance imaging; WM, Waldenström's macroglobulinaemia.

cardiac toxicity [46]. Bortezomib-containing regimens may be considered as primary choices for patients with very high IgM levels or hyperviscosity [III, B].

Combinations with more intensive chemotherapy (e.g. R-CHOP) or nucleoside analogues [fludarabine/rituximab (FR) or fludarabine/cyclophosphamide/rituximab (FCR)] can induce high response rates but with significant toxicity and are therefore not primary options for first-line treatment of WM [III, D] [33, 37].

The use of single-agent therapy with alkylating agents or nucleoside analogues or rituximab is associated with low response rates and is only considered for patients with comorbidities that preclude the use of more effective chemoimmunotherapy combinations. Rituximab has low toxicity but is associated with modest response rates as a monotherapy [III, B]. As a single agent, oral fludarabine is more effective than chlorambucil [I, B] [47].

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has substantial activity and is associated with high response rates in pretreated patients with WM, characterising it as the most active single agent in WM [17, 18]. Ibrutinib has been approved by the European Medicines Agency (EMA) for patients with WM who have relapsed after primary therapy and for the first-line treatment of patients who are 'not eligible for chemoimmunotherapy'. The results of the iNNOVATE study were recently published, in which the combination of ibrutinib with rituximab was compared with rituximab monotherapy in patients who had received no previous treatment or in pretreated, rituximab-sensitive patients [48]. At 30 months, the PFS rate was 82% with ibrutinib/rituximab versus 28% with placebo/rituximab [hazard ratio (HR) 0.2, 95% confidence interval (CI): 0.11–0.38] with at least a partial response (PR) in 72% versus 32% of patients; the advantage for PFS was also seen in patients previously untreated

Table 7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III Prospective cohort studies
IV Retrospective cohort studies or case–control studies
V Studies without control group, case reports, expert opinions

Grades of recommendation

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D Moderate evidence against efficacy or for adverse outcome, generally not recommended
E Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [60].

[HR: 0.34 (95% CI: 0.12–0.95)] [48]. A small phase II study in newly diagnosed patients with single-agent ibrutinib has also been presented recently but with short follow-up [49]. Thus, ibrutinib could be a treatment option for elderly patients with comorbidities not tolerating conventional chemoimmunotherapy, although no full set of data has been published yet for the use of ibrutinib in first-line therapy in any setting (fit or unfit patients) [V, B].

Although maintenance treatment with rituximab could provide some clinical benefit according to retrospective data [50], maintenance therapy cannot be recommended in WM due to the lack of prospective data [IV, D].

Relapsed disease (Figure 2)

Based on the pivotal trial in relapsed patients and on data in rituximab-refractory patients [18], ibrutinib is recommended for patients who relapse within < 1 year after their last treatment, including rituximab-refractory patients [III, A]. Patients with wild-type *MYD88* may have no significant benefit from ibrutinib; however, this observation is based on data from limited numbers of patients. Furthermore, patients with non-*MYD88*^{L265P} mutation may also benefit from ibrutinib therapy [14]. Ibrutinib should be given until disease progression, and relapses are common after discontinuation of the drug. Toxicity is low; however, the risk of certain toxicities, such as atrial fibrillation, may be over 10% in long-term therapy.

For patients who relapse between 1 and 3 years, ibrutinib is an appropriate treatment choice. An alternative rituximab-based combination might be considered in patients who are not eligible for ibrutinib or who relapse later in this time period. For patients who relapse > 3 years after receiving a rituximab-based regimen, an alternative rituximab-based combination may be considered. If rituximab with cyclophosphamide was used (i.e. DRC), rituximab with either bendamustine (i.e. BR) or bortezomib either with or without dexamethasone (i.e. BDR or VR) may be used [IV, B] [40]. Rituximab with nucleoside analogues (FR, FCR) is an active but also toxic combination and therefore should be used cautiously [III, C]. For patients who achieve a prolonged remission with their primary therapy (i.e. > 4 years), re-instituting the prior regimen may also be considered [IV, B] [40]. Ibrutinib may also be a treatment option for patients with late relapses.

High-dose therapy with autologous stem cell transplantation (ASCT) has a role for the management of young patients with chemosensitive disease but also early relapse and a clinically aggressive course [IV, B] [51]. In patients having disease transformation to high grade lymphoma, ASCT may also be part of the treatment strategy. The role of allogeneic stem cell transplantation (alloSCT) is limited outside clinical trials and should be considered only in highly selected young patients with aggressive disease, who have failed or are resistant to BTK inhibitors [IV, C] [52, 53].

Response evaluation

Response evaluation in WM is based on serial measurements of monoclonal IgM in the serum and on relative reduction or increase of IgM (Table 5) [21]. Caution is required not to interpret an IgM flare as disease progression. BM assessments are not routinely recommended for response evaluation, except for establishment of CR [21]; however, in the context of clinical trials, it is strongly encouraged to have serial BM assessments. Discordant results in reduction of IgM and BM infiltration have been reported during therapy with several agents [17, 54–56]. Response assessment by imaging (CT, MRI) should only be carried out in patients with baseline lymphadenopathy/organomegaly or extramedullary disease, or if a relapse of the disease with transformation is suspected based on clinical judgment. A PET-CT scan is not indicated in WM.

Personalised medicine

There is ongoing research to identify molecular markers that could lead to personalised medicine. Mutational status of *MYD88* and *CXCR4* may affect response and kinetics of response to ibrutinib [14, 18]; however, limited data exist on how their mutational status may affect the efficacy of other agents or combinations such as chemoimmunotherapy regimens or proteasome inhibitors, thereby

impeding the definition of the optimal treatment approach for different genotypes in WM. In the recently published iNNOVATE study, *MYD88* or *CXCR4* genotype had no significant impact on the efficacy of the ibrutinib/rituximab combination [48]. Treatment decisions in WM should be based on patient characteristics and disease presentation (Table 4).

Follow-up, long-term implications and survivorship

Follow-up should include history, physical examination, blood count, routine chemistry and serum electrophoresis/quantification of IgM every 3 months for 2 years, every 4–6 months for an additional 3 years, and every 6–12 months thereafter, with special attention to transformation and secondary malignancies. Routine imaging is not recommended.

Median survival for younger patients exceeds 10 years; for elderly patients, the median survival is shorter, but a significant proportion will die due to reasons unrelated to the underlying WM [4]. Disease transformation and development of myelodysplasia are not very common, occurring in 2%–6% [47, 57] and in 1%–6% [47, 58] of patients with WM, respectively. Second non-haematological malignancies may also develop in 16%–20%, especially in elderly patients [47, 59].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 6. Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

EKa has received honoraria from Amgen, Genesis Pharma, Janssen, Takeda and Prothena, and research support from Amgen and Janssen; VL has received honoraria from Roche, Janssen, Gilead, Amgen and AbbVie and has reported being a board member for AbbVie, Janssen, Roche and Gilead; MAD has received honoraria from participation in advisory boards for Amgen, Takeda, Celgene, Janssen and Bristol-Myers Squibb; EKi has reported participation in advisory board meetings for Celgene, Roche, Janssen, AbbVie and MCI Pharma and giving educational lectures for Gilead, Roche, Celgene, Janssen and AbbVie; PS has received honoraria for scientific talks and scientific advisory boards from Amgen, Roche, Janssen, Gilead, Karyopharm, Morphosys, CTI BioPharma, Celgen, AbbVie, Takeda-Millennium and Gilead; MJK has received research support from Celgene, Roche and Takeda and has reported being an advisory board member for Roche, Celgene, Novartis, Bristol-Myers Squibb, Gilead and Kite Pharma; AT has reported participation in advisory board for Janssen and AbbVie; CB has received research support from Janssen, Roche and Bayer and honoraria from Janssen, Roche, Bayer, Celltrion, Hexal, Pfizer and AbbVie.

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