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REVIEW

Guideline for diagnosis and treatment of Waldenström's macroglobulinaemia

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On behalf of the HOVON Multiple Myeloma Working Party and the HOVON Lymphoma Working Party

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ABSTRACT

On behalf of the lymphoma and multiple myeloma working parties of the Dutch/Belgian Haemato-Oncology Foundation for Adults in the Netherlands (HOVON), we present a guideline for diagnosis and management of Waldenström's macroglobulinemia (WM). Considering the indolent behaviour and heterogeneous clinical presentation of WM, it is crucial to determine the right indications for treatment, as well as to individualise therapeutic options. There are significant differences from the approach to multiple myeloma or the treatment of other indolent non-hodkgin lymphomas, and these results cannot always be extrapolated. There is a lack of large clinical trials due to the low incidence of WM.

Based on the available data, we provide a practical diagnostic classification, as well as recommendations for first-line therapy and options for treating relapsed disease. Some typical clinical features of WM, such as autoimmune phenomena and "IgM flare" after rituximab treatment, are highlighted.

A more elaborate version of this guideline was published in the "Nederlands Tijdschrift voor Hematologie" (Dutch Journal for Hematology) September 2012.

KEYWORDS

Guideline, lymphoma, MGUS, Waldenström, lymphoplasmacytic lymphoma

INTRODUCTION

In the latest World Health Organisation (WHO) classification (2008), Waldenström's macroglobulinaemia (WM) is defined as a neoplasm composed of small B lymphocytes, plasmacytic lymphocytes and plasma cells, accompanied by a paraproteinaemia of the IgM type, while not meeting diagnostic criteria for other small-cell B-cell malignancies. The term lymphoplasmacytic lymphoma (LPL) refers to WM plus those rare cases lacking the IgM M-protein (more than 95% of all LPLs are WM). In this guideline we will use the term WM, but it is also applicable to all cases of LPL.[1-4]

The Swedish physician Jan Gösta Waldenström (1906-1996) described this disease for the first time in 1944. It is a rare type of lymphoma: worldwide the incidence is approximately 3 per million persons per year. The average age at diagnosis is 65 years.

Although there are a wide range of therapeutic options, WM still remains incurable. Therefore, in asymptomatic patients, a 'wait and see' policy is advocated, such as in other indolent lymphomas. The prognosis is very variable with survival ranging from five to more than ten years. Because WM occurs mainly in the elderly, combined with its indolent course, half of the patients die of a cause other than the lymphoma.

This guideline includes recommendations on the diagnosis as well as the treatment of WM.

DIAGNOSIS AND DIAGNOSTIC CLASSIFICATION

For the diagnosis of WM, an IgM M-protein needs to be present in blood, as well as histological proof of a lymphoplasmacytic infiltrate, virtually always localised in the bone marrow. Depending on whether or not there are lymphoma-related symptoms, this can be classified as a symptomatic WM (with treatment indication) or asymptomatic WM (the latter has a higher risk of progression than IgM monoclonal gammopathy of unknown significance (MGUS)). (See *tables 1, 2* and *3*). Of importance, an IgM paraprotein of any level is not sufficient for the diagnosis WM, since there are several other lymphoproliferative disorders that produce IgM (see differential diagnosis). The IgM level is not predictive for the onset of symptoms, and is also not necessarily a reliable marker for tumour burden.[1-4]

CLINICAL SYMPTOMS, HISTORY TAKING AND PHYSICAL EXAMINATION

Approximately one third of the patients are asymptomatic at diagnosis. The symptomatology of WM is determined by both the tissue infiltration and immunological activity of the lymphoma cells, as well as by the physico-chemical properties and immunological specificity of the monoclonal IgM protein. The clinical presentation of WM is therefore often very different from other malignant lymphomas.

In the workup of WM patients, a thorough review of the systems during medical history taking is very important, as well as a complete physical examination, with special attention for lymphadenopathy, hepatosplenomegaly, neuropathy, autoimmune phenomena and signs of hyperviscosity (for a comprehensive list of symptomatology: see *table 1*).[5]

Table 1. *Symptomatology, frequency and mechanism*

Symptom or sign	Percentage at first diagnosis	Mechanism and/or specific recommendations
Fatigue	±70%	Anaemia Constitutional Consider amyloidosis
Constitutional symptoms (night sweats, weight loss)	20-25%	Constitutional
Lymphadenopathy, hepatosplenomegaly	15-25%	Tumour infiltration
Anaemia	40%	Bone marrow infiltration Haemolysis (cold or warm AIHA) Iron deficiency due to gastrointestinal bleeding
Hyperviscosity: Headaches, blurry vision or visual loss, confusional episodes, epistaxis	15%	Emergency: Get an ophthalmology consult for fundoscopy Consider emergency plasmapheresis When measured serum viscosity is >4.0 cp there is a high risk of hyperviscosity-related events
Bleeding tendency	20-30%	Thrombocytopenia i.e. ITP Acquired von Willebrand disease Amyloidosis
Neurological (mainly polyneuropathy)	20-25%	IgM antibodies against myelin-associated glycoprotein (MAG), ganglioside M1 (GM1) or myopathy (antidecorine antibodies) Amyloidosis
Bing-Neel syndrome: impressive neurological symptoms accompanied by WM localisation in CSF and/or abnormalities on MRI	Rare	Aetiology is uncertain: tumour infiltration or local IgM deposition in cerebro are possible causes
Raynaud's phenomenon (11%), acrocyanosis	Up to 20% cryoglobulinaemia, yet only <5% with associated symptoms 5-10% cold agglutinins	Cryoglobulinaemia Cold agglutination Reminder: immunoglobulins should be obtained in a warm bath to avoid cryoprecipitation and false lowering of serum IgM levels
Gastrointestinal symptoms	Unknown	Amyloidosis or IgM deposition Local tumour infiltration Autonomic neuropathy
Hearing loss	Unknown	Hyperviscosity, sensorineural neuropathy, Tumour localisation, thrombosis
Thrombosis	Unknown	Antiphospholipid syndrome via IgM antibodies
Dermatological: urticaria, papules, dermatitis, vasculitis	<5%	Schnitzler syndrome (nonpruritic urticaria), local tumour infiltration, amyloidosis, cold agglutination/cryo
Renal failure	Rare	Specific IgM-mediated glomerulonephritis, amyloidosis, vasculitis. Consider renal biopsy
Osteolytic lesions	Should not be present	When osteolytic lesions are present consider IgM multiple myeloma as a diagnosis
Recurrent infections	Unknown	Hypogammaglobulinaemia, consider antibiotic prophylaxis or IVIG suppletion

Table 2. *Diagnostic workup (Items in bold font should be done in each new patient)*

Test	Remarks
Serum electrophoresis incl. quantative M-protein; immunofixation **Immuunglobulines IgA, IgM, IgG**	Light chain assay in serum/urine: not indicated Reminder: immunoglobulins should be obtained in a warm bath to avoid cryoprecipitation and false lowering of serum IgM levels in patients with cryoglobulinaemia
Complete blood count, PT, APTT **liver enzymes, renal function**	Iron levels if anaemia is present
Bone marrow biopsy for morphology and immunohistochemistry	Please refer to text Immunophenotyping and cytogenetics are optional, they can be helpful to distinguish WM from other small cell b-NHL
CT thorax/abdomen/pelvis	Recommended for staging before starting treatment
Haemolysis parameters (LDH, haptoglobin, reticulocytes, if positive followed by Coombs test and testing for cold agglutinins)	If anaemia is present
B2-microglobulin and albumin	Prognostic markers
Viscosity measurement and ophthalmology consult	When there is clinical suspicion of hyperviscosity, obtain an ophthalmology consult for fundoscopy Measurement of serum viscosity is useful but the diagnosis of hyperviscosity syndrome can be made on clinical grounds only
Hepatitis C and B serology	Mixed (type II) cryoglobulinaemia is associated with hepatitis C, the association of HCV with WM is unclear Determining HCV and HBV status is relevant before starting therapy.
Myelin-associated glycoprotein (MAG), ganglioside M1 (GM1) antibodies (in PNP) or antidecorine antibodies (in myopathy) neurological evaluation incl. EMG	When polyneuropathy is present, in order to determine its cause (i.e. autoimmune versus amyloidosis)
Targeted biopsy if amyloid is suspected	Abdominal fat aspiration if targeted organ biopsy is difficult. Also test bone marrow biopsy for amyloid

Table 3. *Diagnostic classification*

	IgM MGUS	Asymptomatic WM	Symptomatic WM	IgM-related disorder * refer also to tables 1 and 3
IgM M-protein (serum)	Yes	Yes	Yes	Yes
Lymphoplasmocytic infiltration (bone marrow)	No	Yes	Yes	No
WM-related signs or symptoms*	No	No	Yes	Yes
Approach	Follow-up (infrequently)	Wait and see	Start treatment	Depending on specific manifestation, start treatment if applicable
Risk of progression to WM	1.5% per year	50-60% after 5 year	NA	Unknown

The most common presenting complaint is fatigue, often caused by anaemia. The anaemia is often more pronounced than expected based on the degree of bone marrow infiltration. Haemolysis, 'anaemia of chronic disease' caused by proinflammatory factors, dilution through increased plasma volume, and gastrointestinal bleeding can all contribute to the anaemia.

An increased bleeding tendency (of various origins) occurs in up to 20% of patients. Hepatosplenomegaly and lymphadenopathy occur in only 15-20% of patients. IgM-mediated autoimmune disease is a very distinctive manifestation of WM and can also be the presenting symptom. The most common autoimmune phenomena are neuropathy by anti-MAG (myelin associated glycoprotein) IgM antibodies, and autoimmune haemolysis caused by anti-I or anti-i IgM antibodies with complement activation (cold agglutination).

In about 10% of cases the IgM precipitates when the temperature drops below the 37 °C (cryoglobulinaemia); this is associated with vasculitis, Raynaud's phenomenon and glomerulonephritis. Precipitation of the M-protein into amyloid can lead to organ damage: neuropathy, cardiomyopathy, nephropathy or gastrointestinal problems. It is recommended to pay attention to the family history, since WM is sometimes associated with familial clustering of various lymphoproliferative diseases.[6]

Finally, because of the size of the IgM protein, hyperviscosity syndrome can develop with its typical symptoms: disturbed vision, headache, dizziness, heart failure and neurological complications. When hyperviscosity is suspected, an ophthalmological consult should be obtained to aid in diagnosis.

DIAGNOSTIC EVALUATION

Please refer to *table 2* for recommended diagnostic studies in WM patients.

Bone marrow evaluation

Bone marrow examination (biopsy) is required for the diagnosis, since this lymphoma is preferably, and often exclusively, located in the bone marrow. The infiltration typically consists of small B lymphocytes, plasmacytic lymphocytes and plasma cells (see histology illustrations in *figure 1*).

The typical immunophenotype is: expression of B-cell antigens (CD19/20/22/79a), membrane-bound IgM, and cytoplasmatic IgM in the plasma cells, with absence of IgD, CD23, CD103, and CD10. CD5 is usually negative, if positive chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma should be excluded. Additionally, CD38 and CD27 are often positive. The plasma cells are CD138 positive.[1,4,7]

When immunohistochemistry is performed on biopsy material, immunophenotyping of the bone marrow aspirate is not mandatory. However, in some cases it can be helpful to discriminate WM from other low-grade B-cell lymphomas.

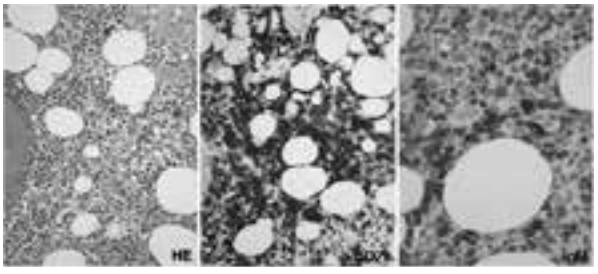
Cytogenetics/molecular markers

Several cytogenetic abnormalities have been described in WM, such as 6q-deletion, and t(9, 14) (p13; q32) both in 40-50% of patients. Recently, Steve Treon *et al.* found a specific point mutation (L265P) in the gene MYD88 (involved in the NFκB cascade) in 27 of 30 patients.[8] However, at this point these findings do not have solid prognostic or therapeutic value. Routine cytogenetic or molecular testing is therefore currently not indicated. Targeted fluorescent in situ hybridisation (FISH) analysis can be helpful if multiple myeloma or follicular lymphoma is suspected; see also the section on differential diagnosis.

Imaging studies

For staging purposes, i.e. before starting treatment, a conventional CT scan of the neck, thorax and abdomen is recommended. A PET scan is not necessary, unless transformation is suspected.

Figure 1. *Bone marrow biopsy with localisation of lymphoplasmacytic lymphoma*



Diffuse infiltration of bonemarrow by small lymphocytes (left). These cells are CD20 positive (middle). Some show plasmacellular differentiation with intracytoplasmatic expression of IgM (right).

CLASSIFICATION OF IGM-RELATED DISORDERS

As for diagnostic classification, WM is somewhere in between non-Hodgkin's lymphomas (NHL) and plasma cell dyscrasias. The WHO classification and important international guidelines are not entirely in agreement.[1,4] For the clinician, it is particularly relevant that in some cases a wait-and-see policy can be applied (IgM MGUS, asymptomatic WM), while in other cases therapy is needed (symptomatic WM, IgM-related conditions) (*table 3*).

IgM MGUS / asymptomatic WM

The risk of progression of IgM MGUS to WM is approximately 1.5% per year. If clear bone marrow infiltration was present (classification: asymptomatic WM) then a treatment indication arose in 6% of patients after one year, 59% after five years, and 68% after ten years in one recent retrospective study.[9,10]

Symptomatic WM and IgM-related disease

In patients with IgM M-protein, bone marrow infiltration and WM-related symptoms, the diagnosis 'symptomatic WM' can be made and treatment is indicated.

Sometimes a very small amount of IgM without evidence of LPL in the bone marrow can cause symptoms, for example amyloidosis, or autoimmune-mediated neuropathy. These patients do not meet the criteria for WM, but do have relevant symptomatology. For these cases, the term 'IgM-related disorder' was introduced. Despite a small tumour load, a treatment indication can occur in these cases, and the choice of therapy is determined mainly by the specific disease manifestation.[4]

DIFFERENTIAL DIAGNOSIS

In the rare cases of LPL without IgM paraprotein (5%), diagnosis can be challenging and depends on the exclusion of other small-cell b lymphomas, such as the marginal zone lymphoma or CLL. Sometimes no definitive diagnosis can be made. When prominent paratrabecular infiltration is found, follicular lymphoma must be considered, which is usually CD10 positive and associated with t(14,18) translocation. When LPL is accompanied by an IgA or IgG type paraprotein, distinction from a multiple myeloma is difficult. Vice versa, multiple myeloma can be accompanied with an IgM paraprotein, although rare. IgM multiple myeloma, unlike WM, usually carries translocation t(11,14), and often features osteolytic bone lesions.

PROGNOSIS

Survival is between five and ten years with a wide range, and there is small group of patients who remain asymptomatic without treatment for a long time (>10 years). The International Prognostic Scoring System for WM (IPSS-WM) gives some idea about the individual prognosis (*table 4*). This scoring system is based on pre-rituximab patient data, but has since been validated in at least one study. The IPSS score does not help in making treatment decisions, but can be important when comparing outcomes of patients in clinical trials.[11]

TREATMENT

Because WM is rare and randomised studies are mostly lacking, it is not easy to establish evidence-based guidelines for treatment. This also applies to the choice of first-line therapy. Some recently published reviews summarise the published data (mostly retrospective series) on effectiveness.[2,3,5,12-14]

When choosing treatment it is important to realise that there are many options available, and that therapy needs to be adapted to the individual patient, taking into account age, life expectancy, (co)morbidity (i.e. neuropathy) and clinical need for rapid response (i.e. hyperviscosity).

Plasmapheresis and prevention of IgM flare

When a patient presents with hyperviscosity syndrome, there is an indication for plasmapheresis, and treatment with a rapid-acting agent should be started in order to halt the production of the M-protein. When serum viscosity is >4.0 cp, there is a high risk of hyperviscosity-related events. Plasmapheresis may also be applied as a preventive measure when rituximab is started in a patient with a total IgM of >40 g/l, to prevent hyperviscosity due to IgM flare. A practical alternative in this situation is to start chemotherapy and only add rituximab once IgM levels are lower.

Table 4. *IPSS-WM]*

Item		Score
Age >65 years		1
Hb <7.2 mmol/l		1
Thrombocyte count <100 x 10^9/l		1
β2-microglobulin >3 mg/l		1
IgM M-protein >70 g/l		1
Risk group	**Score**	**Median survival (months)**
Low	0-1 (except age)	143
Intermediate	2, or age >65 years	99
High	≥3	44

CHOICE OF SYSTEMIC TREATMENT

First-line therapy

Immunochemotherapy: In one of the few randomised studies conducted in patients with WM, Buske *et al.*[15] showed that the addition of rituximab to chemotherapy leads to higher response rates and a longer time to progression in patients with WM. Immunochemotherapy is considered the standard for first-line treatment.

The combination of alkylating agents such as cyclophosphamide with rituximab and steroids is usually a well-tolerated regime. A comparative review article (no randomised studies are available here) showed that the response rates and duration for rituximab-cyclophosphamide prednisone *vs* addition to this regimen of adriamycin and/or vincristine (R-CHOP or R-COP) seem similar, while the last two regimens tend to give more toxicity (mainly neutropenic fever and neuropathy).[16]

A good alternative is DRC: dexamethasone, rituximab, cyclophosphamide, which is less myelosuppressive due to the lower dose of cyclophosphamide, while effectiveness remains high.[17] DRC will be used as the standard arm of the first-line study by the European Myeloma Network.

Also chlorambucil, whether or not in combination with rituximab, is still an option when there is no hyperviscosity or other need for rapid response. Chlorambucil and combination chemotherapy have never been compared head to head. In younger patients, who are potential candidates for autologous stem cell transplantation, the long-term use of alkylating agents such as chlorambucil is not recommended, also because of concerns about the risk of developing myelodysplastic syndromes/acute myeloid leukaemia (MDS/AML).

Rituximab combined with purine analogues (fludarabine, cladribine) with or without cyclophosphamide (e.g. FC-R) is very effective, and often leads to fast responses (median after 2.5 months). In a large randomised study by Leblond *et al.*, which will be published soon, monotherapy fludarabine seems to be more effective than monotherapy with chlorambucil.[18]

Regarding purine analogues, there are concerns about a higher risk of MDS/AML and transformation to aggressive NHL; however, data in WM are somewhat conflicting. It is still advised to give a maximum of 4-6 courses. There are fewer data on cladribine, but it seems equally effective. Purine analogues must be avoided in patients who are candidates for autologous stem cell transplantation.

Every rituximab-containing therapy can cause an IgM flare. Please refer to the plasmapheresis section.

Rituximab single agent and IgM flare: In patients with contraindications for chemotherapy, for example cytopenia or severe neuropathy, single agent rituximab may be an option. However, the chances of response are lower and

responses are very slow compared with the combination of rituximab with (mild) chemotherapy and steroids.[5] Again, the phenomenon 'IgM flare' is of importance: in about half of the patients the IgM rises first, and only starts to drop after four months. The initial rise of IgM after rituximab should not be interpreted as progressive disease! Whether this phenomenon has prognostic implications is unknown.

Treatment of IgM-related disease: polyneuropathy and haemolytic anaemia

These patients do not meet the criteria for WM but have WM-related symptoms and an IgM paraproteinaemia.[4] There is a wide array of rare syndromes, ranging from acquired haemophilia to vasculitis, and they all deserve their own therapeutic approach, although little clinical data are available. We will only discuss the two most common presentations of IgM-related disease, namely polyneuropathy (PNP) and cold autoimmune haemolytic anaemia (AIHA).

Approximately 50% of patients with demyelinating polyneuropathy related IgM paraproteinemia carry anti-MAG antibodies (amyloidosis should also be considered as a cause of PNP in WM patients). Treatment is not always necessary because these PNPs usually progress very slowly. Single-agent rituximab is considered the treatment of choice with responses and symptom relief seen in up to 50% of patients. For patients with rapidly progressive and/or recently diagnosed PNP, immunochemotherapy could be considered because reduction of the IgM will be achieved much faster.[19]

In a cohort of 66 patients with cold agglutination, 50% met the criteria for WM. Almost all of the remaining patients had an IgM paraprotein and in most of them cold agglutination was diagnosed as an IgM-related disorder. Treatment is difficult and again not always necessary. Rituximab monotherapy yields a response in about 50% of patients. When there is no response to single agent rituximab, or when rapid response is needed, there are several options, such as combining it with fludarabine but other combinations of immunochemotherapy could also be considered.[20]

Salvage therapy

The same indications for treatment are applicable (treat only if there is WM-related symptomatology and not just based on a rising IgM) as in the first-line setting. If the response after first-line treatment lasts for more than two years the same treatment can be repeated. If not, one of the other options can be chosen, as mentioned above, or alternatively consider novel agents or transplantation as discussed below.

Bortezomib

Proteasome inhibitors prove very effective in the treatment of WM. Monotherapy with bortezomib gave response rates of approximately 80% in three studies with 64 mostly pretreated patients (e.g. Kastritis *et al.*[12]). The response was quick (1.5 months) while with most classic therapies responses only start after four months. The progression-free survival was at least one year. In a small first-line study using the combination of bortezomib, rituximab, dexamethasone (BRD) even higher response rates were seen, and after two years 80% of patients had no signs of progression.[21]

The main adverse effect is neuropathy (about 70% of patients, up to 30% grade 3, often reversible after dose reduction) and this seems to occur more frequently compared with the use of bortezomib in multiple myeloma. Perhaps using once weekly and subcutaneous dosing may reduce rates of neuropathy. Of course, it is important to pay close attention to neuropathic symptoms and adjust or withhold therapy when necessary. Clinical studies in WM patients are underway with the new proteasome-inhibitor carfilzomib, which seems markedly less neurotoxic. The European Myeloma Network (EMN) is preparing an international study for first-line treatment randomising between DRC and DRC + bortezomib.

Bendamustine

In a large study by Rummel *et al.*, which was presented at the American Society of Hematology Congress in 2009 but has not yet been published, 546 patients with various low-grade lymphomas were randomised to first-line treatment with rituximab-bendamustine versus rituximab-CHOP, including 40 patients with WM. The response rate in patients with WM was very high in both arms (96% and 94%). However, bendamustine was less toxic (fewer infections, no alopecia, and less neuropathy) while the progression-free survival was significantly longer.[22]

In a series of 30 patients with relapsed or refractory WM published by Treon *et al.* bendamustine with rituximab resulted in response in 83% of cases; the median progression-free survival was 13 months. The therapy was well tolerated, the main side effect being myelosuppression, especially in patients who were previously treated with purine analogues. [23]

Based on a small group of patients in two studies bendamustine, combined with rituximab, seems a very effective option with relatively little toxicity. Little is known about the long-term side effects of bendamustine in WM (secondary MDS, stem cell toxicity).

Therapeutic options currently not recommended

There is very little experience with alemtuzumab, and it seems to give much toxicity in patients with WM.[24] Thalidomide has too little effectiveness to be applied as monotherapy. But, it is not so myelosuppressive and when combined with rituximab, results are slightly better. However, there is little experience with this combination

and because of its neurotoxicity thalidomide is not an attractive option in WM. Lenalidomide should not be used, because in WM patients deep anaemia has been described, which also persisted after dose reduction or cessation. (e.g. Kastritis *et al.*[12])

Stem cell transplantation

The majority of patients are not candidates for stem cell transplantation due to age and comorbidity. For a select group of younger and fit patients who relapse quickly after immunochemotherapy, autologous stem cell transplantation can be considered. In a recent series in heavily pretreated WM patients, the non-relapse mortality was 4-6% in the 1st year. The median progression-free survival was about 4 years and after 5 years 60% of patients were still alive.[25, 26]

After allogeneic stem cell transplantation, non-relapse mortality is very high in WM patients: in the largest series 23-40% after 1 year, depending on the conditioning (reduced-intensity or myeloablative, respectively).[27] The five-year progression-free survival was about 45-50% and the overall survival 50-60%. Chronic graft versus host disease was associated with higher non-relapse mortality and lower relapse rates. Considering the available alternatives and the high treatment-related mortality, allogeneic stem cell transplantation should only be considered in the rare young patient with a very aggressive disease course.

Maintenance therapy

There are no prospective studies on the role of maintenance therapy in WM. In a retrospective series 86 of 248 WM patients received maintenance therapy with rituximab: a median of eight doses in the two years after induction therapy with a rituximab-containing regimen. Both the progression-free survival (56 *vs* 29 months) and the overall survival (not reached *vs* 116 months) were better in the maintenance group.

Maintenance therapy with rituximab in WM can be considered after second-line treatment, similar to the approach in other indolent lymphomas.[28]

RESPONSE ASSESSMENT

At the 3rd International WM workshop uniform response criteria were established,[29] which are summarised in *table* 5.

Because the M-protein sometimes responds very slowly, and the level of the M-protein is an unreliable indicator of tumour mass, it is recommended to repeat bone marrow examination when in doubt about the response. Depending on the agent used, lowering the IgM level can be faster (purine analogues, proteasome inhibition) or slower (chlorambucil, rituximab). After chlorambucil therapy, there is often a reduction of clonal B lymphocytes, but the plasma cells remain and may be the source of the persisting M-protein.[30]

Table 5. *Response criteria*

Response	Criteria
Complete response (CR)	Disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy/organomegaly (confirmed by CT scan), along with no signs or symptoms attributable to WM; reconfirmation of the CR status is required at least 6 weeks apart with a second immunofixation
Partial response (PR)	A >50% reduction of serum monoclonal IgM concentration on protein electrophoresis and >50% decrease in adenopathy/organomegaly on physical examination or on CT scan; no new symptoms or signs of active disease
Minor response (MR)	A >25% but <50% reduction of serum monoclonal IgM by protein electrophoresis; no new symptoms or signs of active disease
Stable disease (SD)	A <25% reduction and <25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms resulting from disease and/or signs of WM
Progressive disease (PD)	A >25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings resulting from disease (i.e., anaemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever >38.4 °C, drenching night sweats, >10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinaemia, or amyloidosis) attributable to WM

CONCLUSIONS AND RECOMMENDATIONS

Regarding symptomatology, pathophysiology as well as treatment, WM holds a special position within the low-grade malignant lymphomas. There is definitely room for improvement in treatment results in this relatively rare disease, both regarding effectiveness and toxicity, and therefore it is important to treat patients in clinical trials when possible, stratifying for WM-IPSS score and using uniform response criteria. One of the challenges for the future, as in many non-Hodgkin's lymphomas, is to determine response to treatment faster and more accurately, in order to identify high-risk patients sooner and adjust therapy accordingly.

Because of treatment toxicity, which can be very disease-specific (deep anaemia after lenalidomide, higher risk of neuropathy with proteasome inhibition), clinical experience in treatment of other indolent lymphomas cannot always be extrapolated to WM.[31]

RECOMMENDATIONS FOR CLINICAL PRACTICE

1. WM has a wide range of symptomatology that is partly unique to the disease, and careful history taking, complete physical examination and a targeted diagnostic workup is crucial.
2. Symptoms are not just related to lymphoma infiltration, but often result from the specificity of the IgM paraprotein causing autoimmune phenomena.
3. The level of the M-protein is no reason for treatment if the patient is asymptomatic. Vice versa, a small amount of M-protein can give rise to symptoms and thus be a reason for starting treatment.
4. In patients with hyperviscosity syndrome, plasmapheresis should be started immediately. In addition a rapidly acting therapy to halt IgM production should be instituted. Wait until the IgM has dropped before giving rituximab because of potential IgM flare.
5. As a first-line treatment combination immunochemotherapy is recommended, such as the dexamethasone, rituximab, cyclophosphamide (DRC) regimen, or rituximab plus cyclophosphamide/prednisone (R-CP). Chlorambucil, combined with rituximab and/or steroids, is a good alternative, especially in the older patient.
6. In younger patients (and/or patients who are potential candidates for autologous stem cell transplantation): prolonged use of purine analogues and alkylating agents should be avoided.
7. When starting a WM patient on rituximab, be aware of the phenomenon 'IgM flare'.
8. When a treatment indication emerges two years or longer after first-line treatment, the same treatment can be repeated.
9. When a treatment indication emerges within two years after first-line treatment there is a wide range of active agents and treatment modalities, including autologous stem cell transplantation. Age, life expectancy and comorbidities such as cytopenia and/or neuropathy, will determine which is the preferred choice of salvage therapy in each individual.

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