Waldenström's macroglobulinaemia: Belgian Hematology Society guidelines

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Waldenström's macroglobulinaemia is a B-cell disorder characterised by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy in the blood. This condition belongs to the lymphoplasmacytic lymphomas as defined by the World Health Organization classification (ICD-0 code 9671/3). Approximately one-fourth of patients are asymptomatic. Clinical features of the symptomatic patients are diverse and may relate to overall disease burden (such as peripheral blood cytopaenias, organomegaly and constitutional symptoms) or may be directly attributable to the IgM paraprotein. The latter include hyperviscosity syndrome, amyloidosis, peripheral neuropathy and cold haemagglutinin. Therapeutic options have traditionally involved alkylating agents, nucleoside analogues, and rituximab, either as single therapy or in combination. However, emerging new data on combination therapy as well as novel agents have shown encouraging results. This report provides the Belgian Hematology Society guidelines according to recent clinical studies.
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Introduction

Waldenström's macroglobulinaemia (WM) is a low grade B-cell lymphoma characterised primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of a serum IgM monoclonal gammopathy of any concentration. This condition belongs to the lymphoplasmacytic lymphomas (LPL) as defined by the World Health Organization classification. Most cases of LPL are WM, with less than 5% of cases being IgA, IgG and non secreting LPL. WM has an overall incidence of approximately three per million persons per year.[1] The median age varies between 63-68 years, and 55-70% are male.[2] WM is predominantly a sporadic disease, but up to 20% of patients has at least a first degree relative with a B-cell neoplasm. Currently, systematic screening of family members is not indicated. The main risk factor for the development of WM is a pre-existing IgM-monoclonal gammopathy of undetermined significance (MGUS) with an estimated annual progression rate of 1.5%.[3] Patients with a personal or family history of an autoimmune, inflammatory disorder or a history of hepatitis C (HCV) exposure have an increased risk to develop WM. This association is particularly strong for Sjögren's syndrome and autoimmune haemolytic anaemia (AIHA).[4,5]

Clinical features

WM is a heterogeneous disease in terms of clinical

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Practice Guidelines

Diagnostic condition/ Property of IgM monoclonal protein	Clinical manifestations
Table 1. Morbidities mediated by the monoclonal IgM protein in WM.	
Hyperviscosity	Headaches, blurred vision, epistaxis, retinal hemorrhages, leg cramps, impaired mentation, intracranial hemorrhage
Cryoglobulinaemia	Raynaud phenomenon, purpura, cold urticaria, arthralgias, renal failure
Peripheral neuropathies (antibodies to myelin-associated glycoprotein (MAG), ganglioside M1(GM1), cryoglobulinaemia)	Sensorimotor neuropathies, painful neuropathies, ataxia
Cold agglutinins	Hemolytic anaemia, Raynaud phenomenon, livedo reticularis
Tissue deposition as amorphous aggregates	Bullous skin disease, papules, Scnitzler syndrome, diarrhea, malabsorption, proteinuria, renal failure
Amyloidosis	Fatigue, weight loss, edema, hepatomegaly, macroglossia, organ dysfunction: heart, hepatic and renal failure, peripheral and autonomic neuropathy

manifestations, with 25% of patients being asymptomatic. Morbidity associated with WM is typically due to tissue infiltration by neoplastic cells and/or the physicochemical and immunologic properties of the monoclonal IgM (*Table 1*). The most common clinical presentation is cytopaenia, specifically anaemia related to massive bone marrow infiltration by tumour cells. Fatigue is also a common symptom that is multifactorial, caused partially by the underlying anaemia. Patients may present with symptoms of hyperviscosity related to elevated IgM levels leading to headache, blurry vision and/or epistaxis. Unlike most indolent lymphomas, splenomegaly and lymphadenopathy are present in a minority of patients (15%).[1] Renal function should be carefully evaluated in WM patients because of possible light chain or amyloid deposition, as well as parenchymal involvement by lymphoplasmacytic cells.

Diagnostic workup

To establish a diagnosis of WM, it is necessary to demonstrate an IgM monoclonal protein along with histological infiltration of bone marrow by lymphoplasmacytic cells. There is no minimal serum IgM level or a minimal percentage of bone marrow infiltration to establish the diagnosis of WM, because patients can be symptomatic even at low levels of IgM or with minor bone marrow involvement.

Laboratory assessment
IgM paraprotein should be demonstrated by serum protein electrophoresis and quantitated by densitometry.

Concentration of IgG and IgA should also be measured at diagnosis because low IgA and IgG levels are often present and may contribute to recurring infections.[1] Serum IgA and IgG levels seldom return to normal after treatment, even in good remissions. This may be a reflection of a constitutional defect in plasma cell development.[6]
The value of serum free light chain (SFLC) and Hevylite™ assays (HLC) have not been established and are not essential for the routine assessment of WM patients.[7,8] Cold agglutinins, cryoglobulins, and anti-myelin associated glycoprotein (anti-MAG) should be performed according to the clinical scenario.
Screening for hepatitis B (HBV) and HCV is required prior to the introduction of rituximab-containing treatments and because of the possible association between HCV, WM and cryoglobulinaemia.

Bone marrow assessment
The demonstration of bone marrow infiltration by a lymphoplasmacytic cell population is essential to the diagnosis of WM. This is characterised by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation, including the presence of intranuclear pseudoinclusions (also called Dutcher bodies). A trephine biopsy is recommended to assess the degree and pattern of infiltration accurately and morphology should be supported by immunophenotypic studies. Phenotyping is usually performed on the B-cell component of the disease and cells express pan B-cell markers including CD19, CD20, CD22 and surface IgM, but lack CD23,

Table 2. International Prognostic Scoring System (IPSS) for Waldenström's macroglobulinaemia.			
	Low risk	Intermediate risk	High risk
Age	<65yr	>65 yr	>65 yr
Hemoglobin≤11,5g/dL			
Platelet≤100x10⁹/L	≤1 factor	2 factors	>2 factors
Beta2-microglobulin>3 mg/L			
IgM>7g/dL			
Survival at 5 yr	87%	68%	36%

CD10, CD5 and cytoplasmic Ig. Variations from this phenotypic profile can occur and up to 20% of cases may express CD5, CD10, or CD23. In such cases, chronic lymphocytic leukaemia (CLL) and marginal zone cell lymphoma (MZL) should be excluded and expression patterns of CD25, CD22 and CD103 may be helpful.[9,10] Mantle cell lymphoma (MCL) should be excluded in case of CD5 positive phenotype.

Published data on plasma cell immunophenotyping in WM suggest that the antigenic myeloma patterns (CD19-CD45-CD56+) are not seen in WM plasma cells.[10]

Cytogenetic and molecular analysis
Among chromosomal abnormalities observed in WM, deletion of the long arm of chromosome 6 (6q-) is the most frequent, occurring in up to 50% of patients. Most of the recurrent abnormalities encountered are shared with other indolent B-cell disorders, except for the trisomy 4, which is observed in +/- 15-19% of WM cases and appears to be unique to this clinical entity.[11] Cytogenetic analysis might therefore be useful to clarify the differential diagnosis with cases of IgM myeloma or MZL. Prognostic significance of the chromosomal alterations remains controversial in WM.[11] IgH switch region rearrangements (14q32 translocations) are typically absent in WM and may suggest the diagnosis of IgM myeloma.[12] Recent publications have demonstrated a somatically acquired single point mutation (L265P) in the myeloid differentiation primary response gene (*MYD88*) in 90% of patients with WM.[12] This aberration leads to constitutive activation of the oncogenic nuclear factor-kB signalling pathway. The determination of the *MYD88* mutation status might also help to make the differential diagnosis between WM and MZL.[13,14] CXCR4

is a chemokine receptor that promotes survival of WM cells. CXCR4 mutations have been reported in roughly 30% of WM patients.[59] Although identification of those mutations are not routinely recommended, these patients may benefit differentially from novel therapies (see future perspective). Deletion of *TP53* occurs in a minority of patients and appears to define patients with a poor outcome, but further evaluation is required before use in daily practice.[15]

Imaging
Baseline computerised tomography (CT) scans (chest, abdomen, and pelvis) are recommended in all symptomatic patients prior to the start of treatment. There is no convincing rationale for the routine use of fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, except if histological transformation is suspected.[16]

Differential diagnosis
An IgM monoclonal component accompanied by bone marrow infiltration with lymphoplasmacytic cells can be observed in other B-cell lymphoproliferative disorders, such as MCL, MZL and CLL.[17]

Prognostic scoring system and indication for therapy
The International Prognostic Scoring System for WM (ISSWM) is based on five key adverse prognostic features: age >65 years, haemoglobin (Hb) <11,5 g/dL, platelet ≤100x10³/mm3, β2 microglobulin >3mg/L and paraprotein >70g/L and is presented in *Table 2*.[18] There is consensus that ISSWM should be recorded in all patients at presentation, but there is no evidence to support its use in determining treatment approaches for individual patients.

Table 3. Response criteria from the VI International Workshop on Waldenström's macroglobulinaemia.

Response	Criteria
Complete response (CR)	Absence of serum monoclonal protein by immunofixation Normal serume IgM level No bone marrow involvement Complete resolution of extramedullary disease i.e., any adenopathy/organomegaly, along with non signs or symptoms attribuable to Waldenström's macroglobulinaemia.
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline * Complete resolution of extramedullary disease i.e., any adenopathy/organomegaly, along with non signs or symptoms attribuable to Waldenström's macroglobulinaemia.
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but <90% reduction of serum IgM level from baseline* Rection of extramedullary disease if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but <50% reduction of serum monoclonal IgM level from baseline* Non new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum monoclonal IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease

The indications for treatment include constitutional symptoms, symptomatic adenopathy or organomegaly, disease-related cytopaenia (Hb <10 g/dL, platelet <100x10^3/mm3), hyperviscosity, amyloidosis, symptomatic peripheral neuropathy, symptomatic cryoglobulinemia, or cold-agglutinin disease.[19] Initiation of therapy should not be based on serum monoclonal protein levels as such. Asymptomatic patients may have an indolent course for a long period of time, even when their monoclonal protein exceeds 30g/L.[20] Close observation rather than therapy is appropriate for these patients (*Table 2*).

Response assessment

Treatment responses should be defined using the uniform treatment response criteria recently updated at the VIth international workshop on WM (*Table 3*).[21]
The quality of response does appear to affect outcome.[22] One should be careful to use IgM as a surrogate marker of disease because of possible fluctuations independent of tumour cell killing and because there's not always an association between clinical benefit and IgM response.

This is particularly observed with the use of newer biologically targeted agents such as rituximab and bortezomib. Rituximab can induce a flare in serum IgM levels that may last weeks to months.[23] Purine analogues and alkylators selectively deplete the CD20+ B-cell component with sparing of the CD138+ plasma cell component and induce slow IgM responses. Conversely, bortezomib can suppress IgM levels in some patients independent of tumour cell killing.[24,25]
Therefore, besides the serum IgM levels, repeated bone marrow biopsy and CT scans should be encouraged to refine response assessment and clarify the patient's underlying disease burden.
Assessment of SFLC and HLC may provide an earlier indication of both response and progression, but without prospective evaluation their routine use cannot be recommended.[8]

Treatment approaches to Waldenström's macroglobulinaemia

To date there's no curative therapy for WM. Treatment is started to control symptoms and prevent organ damage.

Several products have shown to be effective but there's a lack of large prospective, randomised trials. This makes it difficult to compare regimens and to set up a general approach. The choice of therapy is generally decided based upon age, general condition of the patient, the severity of the symptoms and eligibility for autologous stem cell transplantation (SCT).

Patients with indolent disease
At least 25% of patients are asymptomatic at the time of diagnosis. Patients that do not have constitutional symptoms, bulky disease, cytopaenias or symptoms due to the IgM monoclonal protein are considered to have indolent disease and have no need for immediate treatment. Fifty percent of these patients will not require therapy within the first three years.[26,27] Observational studies have proven that the watch-and-wait approach in asymptomatic patients is safe. Former studies have shown a better quality of life in those selected patients and no adverse effect on overall survival. There's also no evidence of a negative influence on response to future therapy. However, follow-up should consist of clinical examination and blood analysis every three to six months.[28]

Patients who need urgent therapy
Patients presenting with symptoms due to hyperviscosity, cryoglobulinemia or autoimmune related cytopaenias are in need of urgent treatment. The goal for these patients is to achieve a fast reduction of the IgM paraprotein, which can be reached by therapeutic plasma exchange (TPE). In case of hyperviscosity, red blood cell transfusion should be avoided or planned at the end of a TPE session to prevent an exacerbation of hyperviscosity. TPE is generally performed on a daily basis until symptoms subside or until plasma viscosity is normal. Because IgM is 80% intravascular serum, viscosity rises steeply with increasing IgM levels. Thus, a relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity. TPE reduces viscosity by approximately 20-30% per session. Generally 1-1.5 plasma volumes are exchanged per session. Fluid replacement usually consists of albumin. According to the American Society for Apheresis (ASFA) guidelines TPE is necessary for patients with symptomatic hyperviscosity due to a monoclonal gammopathy (evidence level category I, recommendation grade IB). TPE does not change the disease progression and termination of TPE will lead to a new rise of IgM. For this reason it is indicated to associate a general treatment as soon as possible.[29,30]

Frontline therapy
As stated earlier, there is no general agreement on the frontline therapy in WM patients. Several therapies have been shown to be effective as single agents or in combination schedules. Most treatment options are derived from other lymphoproliferative malignancies and include the use of alkylating agents, nucleoside analogues and rituximab. Other options are based on myeloma treatment.
Due to the lack of randomised prospective trials we are also confronted with reimbursement issues in Belgium. Inclusion in clinical trials should be promoted for these patients at any time during disease evolution.
Because of the long natural history of the disease the first treatment regimen should be chosen carefully, taking possible future treatments into account. There is a general agreement to avoid alkylating agents and nucleoside analogues in younger patients because of a possible risk of transformation to high grade lymphoma or therapy related myeloid malignancies and because of the toxic effects to stem cells.[31,32]

Rituximab as single agent and in combination with cyclophosphamide based regimens
The use of rituximab has become a standard of care in WM because of the low incidence of toxicities, the non-myelosuppressive character and the absence of a toxic effect on stem cells. However, rituximab can be associated with a paradoxical rise in IgM, the so-called IgM-flare phenomenon. Therefore one should be alert to hyperviscosity symptoms and the introduction of rituximab should be deferred in patients at risk for hyperviscosity (IgM above 40 g/L). Pre-emptive TPE before rituximab may be considered for patients with IgM ≥50 g/L (evidence level category I, recommendation grade IC) in order to avoid symptomatic IgM-flare. Rituximab as a single agent in first-line treatment is disappointing for patients with a high tumour burden. The response rate is not higher than 50% and there is only a limited effect on progression free survival (PFS).[33,34] However, rituximab as a single agent can be a good treatment option in low risk patients with moderate cytopaenia, IgM-related neuropathy or autoimmune mediated cytopaenia (unresponsive to corticosteroids). It is important to notice that the optimal response to rituximab may not be seen for months (twelve to eighteen months) and early evaluation may result in an underestimation of response. Combining rituximab with other agents improves response rates and PFS. As frontline treatment the majority of patients receive
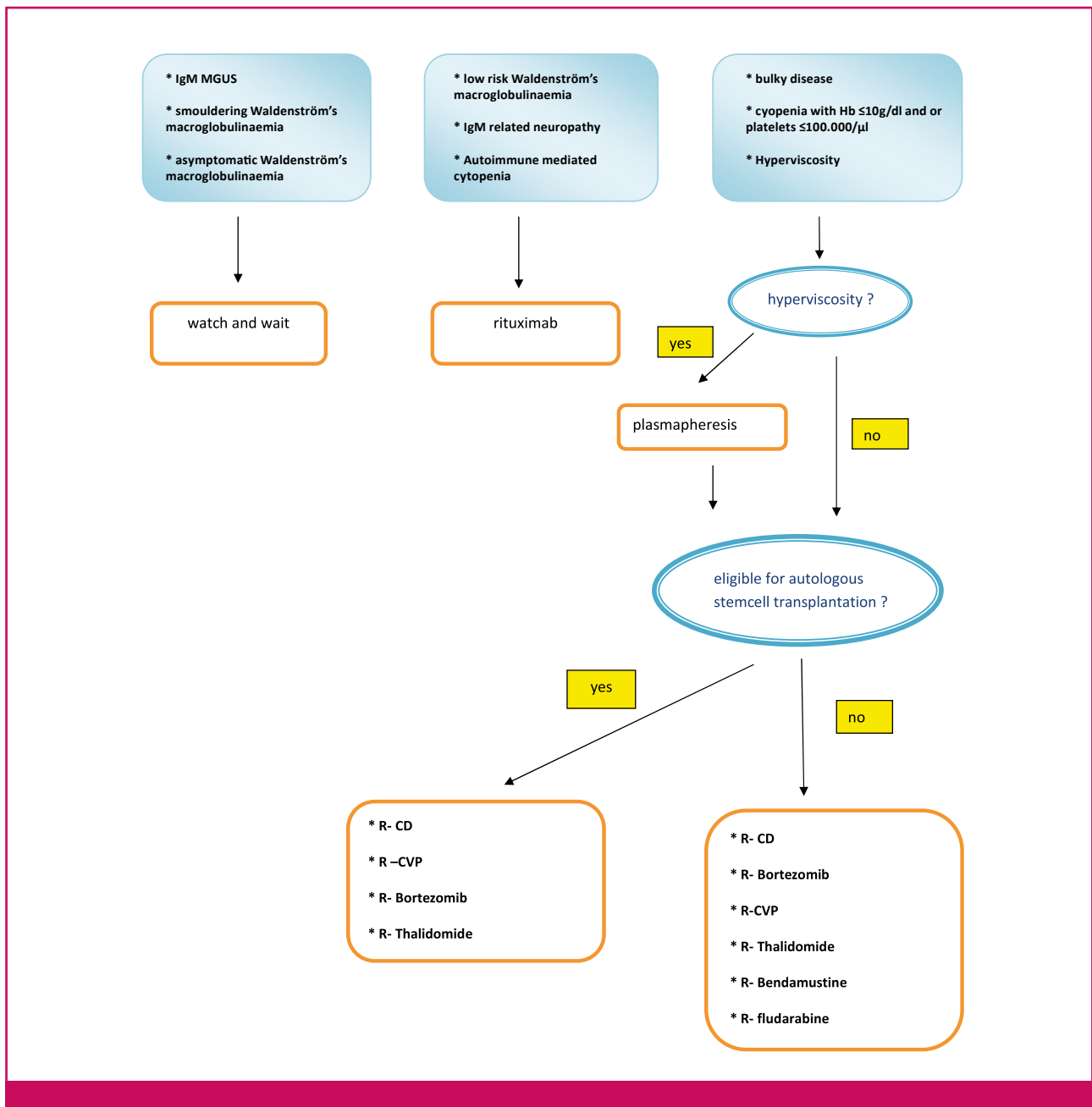
Figure 1. Treatment of newly diagnosed Waldenström's macroglobulinaemia.

a combination of rituximab with a cyclophosphamide based regimen: rituximab- cyclophosphamide- dexamethasone (R-CD) or rituximab- cyclophosphamide- prednisolone (R-CP). These schedules give overall response rates of 70-80%, and complete responses in approximately 10% of patients.[35-37] Despite the widespread use of CHOP, there has been a lot of debate about the necessity of including doxorubicin and even vincristine in the treatment for WM. Schedules without anthracycline and vincristine have proven to be equally effective with fewer adverse events, particularly treatment-related neuropathy and febrile neutropaenia.[36]

Bortezomib

Bortezomib is a potent, reversible proteasome inhibitor. In vitro activity has been demonstrated in WM cell lines. A phase II trial using single agent bortezomib showed a 25% reduction of IgM level in 78% of patients, generally seen during the first cycle. However, nodal response was less and overall response, considering IgM reduction with nodal response was only 26%.[38] Bortezomib combinations have been evaluated as upfront therapy in two phase II studies. In a small trial, weekly bortezomib (six cycles) in combination with rituximab during the first four cycles has shown response in 65%

of patients and median time to progression was not reached (at a median follow-up of fourteen months). Grade 3 and 4 toxicity was mainly haematological and no grade 3 or 4 neuropathy was seen (probably because of the weekly administration of bortezomib).[39] In a recent update of a large phase II trial combining bortezomib, rituximab and dexamethasone (BRD), an overall response of 85% with a median PFS of 42 months was determined. The BRD regimen achieves rapid disease control with a median minimum response observed at 1.1 months.[40] Prophylaxis for herpes zoster infections is mandatory and patients should be carefully monitored for neuro-pathy. Neuropathy was seen less frequently and was less serious when bortezomib was given weekly and/or subcutaneously.
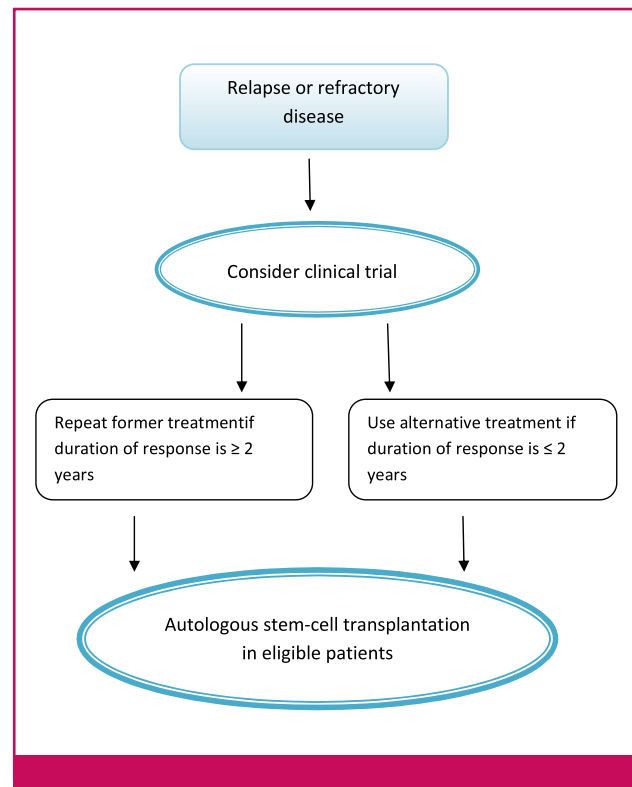
Nucleoside analogues

Nucleoside analogues have been used as monotherapy for the treatment of WM and have been proven to be effective both as frontline and as salvage therapy. In a phase III trial, oral fludarabine was superior to chloram-bucil in newly diagnosed WM with an overall response rate of 48%, a median PFS of 36.3 months and a duration of response of 38.3 months.[41]

Combining fludarabine with rituximab enhances the response rate to 86% and the median PFS to 51 months.[42] Tedeschi et al. reported a response rate of 79%, with 12% complete remission and 21% very good partial re-sponse in a group of 43 patients with symptomatic WM treated with fludarabine, cyclophosphamide and rituximab.[43] The addition of cyclophosphamide might however evoke more adverse events (grade 3/4 neutro-penia in 44% of the patients).

Retrospective studies warned about a higher incidence of disease transformation (6%) and development of tMDS/AML (1.5%) with the use of nucleoside analogues.[31] The fifteen year probabilities of developing disease transformation or tMDS/AML was respectively 21% and 8% in patients treated with nucleoside analogues. A recent phase III trial (chlorambucil versus fludarabine) did not confirm these data but the median follow-up in this trial was 36 months.[41]

Nucleoside analogues should also be avoided in patients eligible for autologous SCT because they might impede stem cell mobilisation.[44] Nevertheless, response rates with fludarabine combinations are high, even in patients with relapsed or refractory WM and the duration of response is long. Therefore, fludarabine-based combi-nations could be considered in patients with relapsed/refractory WM with a good performance status.

Figure 2. Treatment algortihm for relapse/refractory disease.

Alkylating agents

Bendamustine

Bendamustine is an old alkylating agent with nucleo-side analogue properties that has recently been redis-covered. A trial by Rummel et al. showed the results of 22 WM patients treated with bendamustine-rituximab (BR) and nineteen patients treated with R-CHOP as first-line therapy.[45] Responses were similar (95% in both arms with 60% complete response), but BR was superior in terms of median PFS (69.5 versus 28.1 months) and toxicity was generally lower than seen with R-CHOP. Regarding stem cell harvest, after six cycles of BR, the CD34+ yield was similar to that after R-CHOP.[53] Other clinical trials with bendamustine as a treatment option for low grade lymphoma, including patients with WM, revealed similar results. Therefore, BR is now a primary treatment option, especially for patients with high tumour bulk.

Chlorambucil

For older, unfit patients presenting with slow progressing disease, chlorambucil may still be an option because of the good tolerance and ambulatory follow-up. Two pros-pective trials explored the use of chlorambucil as single agent. In the trial of Leblond et al., the ORR of chloram-bucil was 38.6% with a median PFS of 27.1 months.[41]

The second trial, comparing continuous or pulse therapy noted a response rate of 79% in the patients with continuous treatment.[46] Responses are slow and treatment should often continue longer than six months.

Immunomodulatory drugs
Thalidomide
The Waldenström's Macroglobulinaemia Clinical Trials Group (WMCTG) conducted a trial with thalidomide (400 mg/day) in combination with rituximab (eight administrations). Responses were comparable to immunochemotherapy and varied between 70-80%. Median PFS was three years. However, frequent neuropathy necessitated thalidomide dose reductions or therapy discontinuation.
Because of the low level of myelotoxicity, thalidomide-rituximab is a good treatment option for patients presenting with myelosupression.[47,48]

Lenalidomide
Lenalidomide was also tested in combination with rituximab. However, the trial was prematurely terminated because of serious adverse events (acute, severe anaemia).[49] It is advised not to use lenalidomide in WM outside clinical trials.

Treatment of relapsed or refractory disease
Treatment options for patients with relapsed disease include reinstitution of the initial treatment, switch to an alternative treatment regimen or high dose chemotherapy followed by autologous SCT. Patients should be encouraged to participate in clinical trials if available. A possible algorithm for the treatment of patients with relapsed disease is presented in *Figure 2*.

Autologous SCT
Several clinical studies have examined the feasibility and safety of high dose conditioning regimens followed by autologous SCT. The European Bone Marrow Transplant Registry (EBMTR) reported the results of 202 patients who received an autologous SCT. The five year PFS and overall survival rates were 31% and 61%, respectively. The treatment-related mortality was 6%.[47] Other smaller trials showed similar results. Chemosensitivity at the moment of autologous SCT was the most important prognostic factor for non-relapse mortality (NRM), response rate, PFS and overall survival.[50] Autologous SCT is a valuable option for younger patients with relapsing high risk disease. As part of primary therapy, autologous SCT could be considered in selected young patients with high risk IPSSWM and elevated lactate dehydrogenase.[53] Patients with ≥3 lines of prior therapy appear to have limited benefit from autologous SCT.

Allogeneic SCT
Information regarding allogeneic SCT in WM is limited. Initial series included mainly heavily pretreated patients and used myeloablative conditioning (MAC). In those small series, long-term CR was reported suggesting a graft-versus-WM effect, but this was associated with high transplant-related mortality (40%). The Lymphoma Working Party of the EBMT recently published a large series of 86 patients that underwent allogeneic SCT.[52] The conditioning was myeloablative in 37 patients and reduced-intensity (RIC) in 49 patients. Overall response rate was 75.6%. PFS and OS at five years was 56% and 62% for MAC and 49% and 64% for RIC, respectively. NRM at three years was 33% for MAC and 23% for RIC. Chronic GVHD was associated with higher NRM, but also with lower relapse rate. In general this translated into an improvement of PFS (non significant).[50,51] Given the advanced stage of the disease (55% had failed three or more lines of therapy) these results should be considered as promising and confirmed the graft-versus-WM effect. Therefore, allogeneic SCT can be considered as a treatment option for younger high risk patients who have a good performance status and with relapse/refractory disease. However, taking into account all the new treatment options and the high morbidity and mortality associated with allogeneic SCT, this should be performed in a clinical trial when possible.[50]

Future perspectives
Several novel agents are currently under study in relapse/refractory WM patients.

Everolimus
Everolimus is an oral inhibitor of the mTOR pathway. Long-term results of a phase II study of everolimus were recently reported in a large cohort of patients with relapsed/refractory WM. The overall response rate was 50% and 23% of patients achieved a major response. Clinical benefit was seen in 73% of the patients. The median duration of response has not been reached and median PFS was 21 months. At one year, 67% of patients remain progression free.[54] Tolerance to therapy in this series was good, and a clinical trial examining the activity of everolimus in previously untreated patients with WM has recently been initiated.

Key messages for clinical practice

1. Waldenström's macroglobulinaemia-patients without IgM-related pathology and/or organ dysfunction should be observed rather than treated.

2. Plasmapheresis should be considered in patients with symptomatic hyperviscosity and before the start of rituximab if IgM exceeds 50g/L, but also in patients with IgM-related neuropathy, severe cryoglobulinemia, and cold agglutinin disease.

3. A rituximab-containing frontline treatment is recommended in symptomatic Waldenström's macroglobulinaemia. Depending on the clinical situation, R-CD, R-CP, BR, BRD and R-Thalidomide, are all efficacious treatment options. Single agent rituximab, oral fludarabine or chlorambucil may be considered in older patients with slow disease progression, poor performance status or major comorbidities.

4. Nucleoside analogues should be avoided in young patients.

5. At relapse, retreatment with the previous therapy may be appropriate depending on the duration of response and pre-existing toxicities.

6. Autologous SCT is a salvage therapy for selected patients with chemosensitive disease. The place of allogeneic SCT is less defined and should not be used outside a clinical trial setting.

Novel proteasome inhibitors (Carfilzomib)

Carfilzomib, a second-generation proteasome inhibitor, was recently evaluated in combination with rituximab and dexamethasone (CaRD), mainly in untreated WM patients. The schedule of carfilzomib was attenuated (days 1, 2, 8, and 9) compared to myeloma dosing, and maintenance therapy (days 1 and 2 only) was given every eight weeks for eight cycles. The overall response rate was 87% with a PFS of 65% after a median follow-up of 15.4 months. CaRD therefore represents a novel neuropathy-sparing option for proteasome inhibitor-based therapy for WM.

Ofatumumab

Ofatumumab, a fully human monoclonal anti-CD20 antibody, was investigated as first-line treatment in relapsed/refractory patients. Responses were higher in treatment-naïve (6/9, 67%) and rituximab-naïve (9/12, 75%) patients compared to rituximab-exposed patients (13/25, 52%). Infusion-related reactions were common and, as with rituximab, IgM-flare was observed.[56] Ofatumumab has a promising activity but more data are needed in rituximab-refractory disease and combinations with other agents are under investigation.

Ibrutinib

The identification of the common somatic mutation in *MyD88* in WM offered the opportunity for a more targeted approach. Bruton's tyrosine kinase (BTK) has a critical place in signalling transduction through the MyD88-IRAK signalling pathway. Ibrutinib, a selective BTK inhibitor, has shown high activity in MyD88-mutated cell lines. Treon et al. reported the preliminary results of ibrutinib in patients with relapsed/refractory disease at ASH 2013. With a median follow-up of six cycles, the best overall response rate was 81% (4 VGPR, 32 PR, 15 MR), with a major response rate (PR or better) of 57.1% and a median time to response of four weeks.[57] Rapid reductions in IgM serum and improved haemoglobin occurred in most patients receiving ibrutinib. Main adverse events were thrombocytopenia, neutropenia, stomatitis and bleeding. WHIM-like mutations in CXCR4 are present in 1/3 of patients with WM, and their expression induces BTK activity and confers decreased sensitivity to ibrutinib in WM cells.[57,58] The use of CXCR4 inhibitors such as plerixafor might be promising for the treatment of WM patients with mutated CXCR4.

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For the complete list of references we refer to the electronic version of this article which can be downloaded from www.ariez.com.

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