REVIEW ARTICLE

Monoclonal IgM Gammopathy and Waldenström's Macroglobulinemia

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SUMMARY

Background: 3.2–3.5% of persons over age 50 have a monoclonal gammopathy. Monoclonal gammopathies have many causes, including cancer. 10–20% of monoclonal gammopathies are of isotype IgM. A systematic approach to the differential diagnosis of IgM gammopathies is essential because of the different therapeutic implications of the various underlying conditions.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed and current guidelines from Germany and abroad.

Results: The diagnosis of a monoclonal IgM gammopathy is established by serum electrophoresis in combination with immune fixation. Further evaluation enables the identification of the underlying condition: the differential diagnosis includes IgM-MGUS (monoclonal gammopathy of unclear significance), Waldenström's disease, and IgM myeloma. The therapeutic implications of the underlying condition vary from watchful waiting in IgM-MGUS to combined rituximab and antineoplastic chemotherapy (off-label first-line use of rituximab) in symptomatic Waldenström's macroglobulinemia. Ibrutinib has been approved for the treatment of patients with recurrences, or of those for whom first-line treatment with rituximab and chemotherapy is not suitable. The current treatment options do not result in cure. In symptomatic Waldenström's disease, the goal of treatment is to keep the disease under control for as long as possible without impairing the patient's quality of life.

Conclusion: Evidence-based treatment decisions in Waldenström's macroglobulinemia now rely mainly on small-scale, single-armed trials. Patients with this disease should be treated in the setting of a clinical trial if possible. Trials aimed at improving the quality of treatment for other IgM-associated diseases, such as IgM neuropathies and cold agglutinin disease, would also be desirable.

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Monoclonal gammopathy, which is often an incidental finding, is found in 3.2–3.5% of individuals aged over 50 years. The majority of individuals (70%) develop IgG monoclonal gammopathies, followed by IgM gammopathies (10–20%). IgA gammopathies (10–17%) and biclonal (the presence of more than one monoclonal immunoglobulin) gammopathies (3–5%) are rarer (1, 2). Serum electrophoresis is recommended as a screening test in patients with:

- Elevated erythrocyte sedimentation rate (ESR), acute or chronic inflammation
- Suspected monoclonal gammopathy
- Unexplained blood count changes (anemia, cytopenia)
- Suspected kidney disease (e.g., nephrotic syndrome)
- Suspected liver disease (e.g., cirrhosis)
- Polyneuropathy
- Changes in total protein level
- Suspected tumor (e.g., carcinoma)
- Suspected congenital or acquired immune defect
- Hypercalcemia (3).

In the case of an elevated γ -fraction (M gradients) on serum electrophoresis, immunofixation of serum and urine should be performed in a first step to differentiate between monoclonal and polyclonal gammopathy and to identify IgM gammopathy. If monoclonal IgM gammopathy is identified, monoclonal IgM needs to be quantitatively determined by means of the optical techniques nephelometry or turbidimetry, whereby the scattering and attenuation of a light beam due to serum turbidity caused by the antibody can be measured. The quantitative determination of IgM is relevant for follow-up investigations, e.g., particularly in Waldenström's macroglobulinemia (WM) during or following treatment. Where possible, quantitative determinations should be consistently carried out with one of the two methods, since nephelometry often measures higher levels than does turbidimetry (e1). It should be noted that, due to increased plasma volume and strongly elevated IgM, falsely low hemoglobin levels may be measured.

Once monoclonal IgM gammopathy has been confirmed, the question arises as to the causes of this laboratory finding. The aim of this review is to provide readers with an overview of the differential diagnoses of monoclonal IgM gammopathy, as well as of the

BOX 1

Differential diagnoses of monoclonal IgM gammopathy (modified from [39])

- Monoclonal gammopathy of undetermined significance (MGUS)
- Waldenström's macroglobulinemia
- Other indolent lymphomas (CLL [SLL], follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma)
- IgM myeloma
- IgM amyloidosis
- IgM-related disorders:
 - IgM neuropathies
 - Cryoglobulinemia (type I and type II)
 - Cold agglutinin disease
 - POEMS syndrome
 - Schnitzler syndrome
 - Pyoderma gangraenosum
 - Scleromyxedema
 - Monoclonal gammopathy of renal significance

CLL, chronic lymphocytic leukemia; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-gradient, skin lesions; SLL, small-cell lymphocytic lymphoma

treatment of its causes, particularly since considerable progress has recently been made in the diagnosis and treatment of underlying diseases such as WM.

Methods

A selective literature search of national and international guidelines was carried out in PubMed in May 2017 with no retroactive time limits. Own study data were taken into account.

Differential diagnoses

IgM MGUS

The most frequent differential diagnosis (*Box 1*) in the presence of a monoclonal IgM paraprotein is monoclonal gammopathy of undetermined significance (MGUS). MGUS can be classified into IgG, IgA, and IgM MGUS, as well as the rare light-chain MGUS, according to the isotype of the monoclonal immunoglobulin. With a relative percentage of 10–20% of all monoclonal gammopathies, IgM MGUS is defined by an IgM serum protein of less than 3 g/dL, less than 10% clonal lymphoplasmacytic cells in bone marrow, and the absence of symptoms typical of WM (*Table 1*). The risk of MGUS progressing to a malignant lymphoproliferative or related disease is 10% within the first 5 years following diagnosis (4). However, many patients remain asymptomatic lifelong. It has been demonstrated that at least 50% of patients with IgM MGUS already carry *MYD88* mutations. An additional *CXCR4* mutation, which is seen in approximately

15–20% of IgM MGUS patients, could represent a possible genetic progression factor in *MYD88*-mutated patients (5). However, risk stratification is currently based on clinical variables such as the risk score developed by the Mayo Clinic, which is based in turn on epidemiological data. According to this score, the presence of IgM MGUS is associated with a higher risk of progression compared with the more common IgG MGUS (*eTable 1*) (6, 7).

Waldenström's macroglobulinemia

WM is another important differential diagnosis of monoclonal gammopathy. WM is a rare subgroup of indolent B-cell lymphomas. It is defined by a monoclonal IgM serum protein and at least 10% monoclonal lymphoplasmacytic cells in bone marrow (*Table 1*). WM accounts for 1–2% of all hematological neoplasias and has an annual incidence of 3.8 per million persons in the US (8). By definition, it is always associated with IgM paraproteinemia. However, patients with other lymphomas also exhibit IgM gammopathy (20.2% of chronic lymphocytic leukemia [CLL] patients and 7.1% of marginal zone lymphoma patients) (9). Bone marrow histology to detect the obligatory bone marrow infiltration by lymphoplasmacytic lymphoma (LPL) is required to establish the diagnosis of WM (10). The characteristic symptoms are caused by bone marrow infiltration of lymphoma cells on the one hand, and the at times significantly elevated immunoglobulin-M (IgM) paraprotein, which can result in greater blood viscosity or autoimmune phenomena, on the other (11, 12) (*eTable 2*).

WM is a heterogeneous disease not only clinically but also genetically. The most common acquired mutation affects the *MYD88* gene, which is mutated in over 90% of patients. A second common acquired mutation affects the *CXCR4* gene, which carries a genetic change in around a third of patients (13). Three genotypes have been described to date based on these mutations:

- Genotype 1: *MYD88* mutated/*CXCR4* wild-type
- Genotype 2: *MYD88* mutated/*CXCR4* mutated
- Genotype 3: *MYD88* wild-type/*CXCR4* wild-type

Early studies suggest that classifying mutations into genotypes could have clinical implications, since patients with relapsed WM and genotype 3 responded markedly worse to ibrutinib treatment compared with the other genotypes (at least partial remission achieved in 92%, 62%, and 0% for genotypes 1, 2, and 3, respectively) (14, 15).

IgM amyloidosis

Amyloidosis refers to a group of protein-folding disorders. AL-amyloidosis, in which clonal plasma cells secrete amyloidogenic light chains, is associated with hematological disorders. Although AL-amyloidosis with monoclonal IgM gammopathy is a rarity, it should always be included in the differential diagnosis when monoclonal IgM is present. The clinical manifestation of IgM amyloidosis is essentially comparable with that

of non-IgM amyloidosis; however, pulmonary symptoms, polyneuropathy, and lymphadenopathy seem to be more common in the former (16).

IgM-related disorders

The highly heterogeneous disorders (*Box 1*) that fall into this category pose a diagnostic challenge. It is not so much the size of the clonal plasma cell clone that plays a role here, but rather the “toxic” nature of the paraprotein. Some of these diseases are triggered by the deposition of paraprotein (e.g., amyloidosis, type I cryoglobulinemia), while the others are triggered by autoantibody activity of the paraprotein (e.g., cold agglutinin disease, type II cryoglobulinemia, and IgM neuropathies). Relevant bone marrow infiltration is not seen in these patients or only in a small percentage. Two IgM-related disorders will be examined here in more detail (17).

IgM-related polyneuropathy

Of the subtypes of paraproteinemia, IgM monoclonal gammopathy is the most common form to be associated with polyneuropathy. It is assumed that more than 10% of all “idiopathic polyneuropathies” are caused by monoclonal gammopathy. Therefore, serum electrophoresis and immunofixation should always be performed as part of the differential diagnosis of unclear polyneuropathy. Around 50% of IgM gammopathy patients have anti-MAG (myelin-associated glycoprotein) antibodies against a glycoprotein in the myelin sheath of central and peripheral nerves, and which, clinically, are characteristically associated with distal acquired demyelinating sensory neuropathy (DADS-M) (18). A distinction needs to be made here from distal acquired sensory demyelinating neuropathy without anti-MAG antibodies (DADS). This differentiation is potentially relevant in terms of the treatment option selected, since rituximab, for instance, may be a treatment option in patients with DADS-M (18, 19).

IgM-induced cold agglutinin disease

Cold agglutinin disease, which is responsible for 15% of all cases of hemolytic anemia, is also an IgM-related disorder (20, 21). In addition to anemia, patients often present clinically with cold-induced symptoms such as livedo reticularis, Raynaud’s disease, acrocyanosis and, rarely, cutaneous necrosis. An underlying hematological disorder, in most cases MGUS, is the cause of cold agglutinin disease in approximately 80% of patients. Pathophysiologically, hemolysis is a complementary association and mainly takes place extravascularly. Splenomegaly is not typical. The severity of hemolysis depends on the thermal amplitude (i.e., the stronger the agglutinins bind to erythrocytes at a certain temperature) of the antibody: the higher the thermal amplitude, the more pronounced clinical symptoms are. The level of antibody titers, on the other hand, correlates less well with clinical symptoms (22).

TABLE 1

Differentiation of IgM MGUS, IgM-related disorders, WM, and MM (modified from [37, 11])

Criterion	Monoclonal IgM in serum	Bone marrow infiltration	End-organ damage/symptoms
IgM MGUS	<3 g/dL	(<10%)	Negative
IgM-related disorders	Positive (independent of serum concentration)	Generally negative	To some extent
WM	Positive (independent of serum concentration)	Positive (≥ 10%) (LPL)	Positive
IgM MM	Positive (independent of serum concentration)	Positive (≥ 10%) (plasma cells)	Positive (e.g., osteolysis, kidney damage, anemia)

LPL, lymphoplasmacytic lymphoma; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; WM, Waldenström’s macroglobulinemia

BOX 2

Diagnostic work-up to assess monoclonal IgM gammopathy (modified from [40])

• Basic diagnostic work-up

– Patient history and clinical examination

Focus on possible symptoms of multiple myeloma, Waldenström’s macroglobulinemia, amyloidosis, and IgM-related disorders

– Laboratory tests

Complete blood count, differential blood count, creatinine, glomerular filtration rate (GFR), urea, C-reactive protein (CRP), lactate dehydrogenase (LDH), sodium, potassium, calcium, phosphate, β_2 -microglobulin, total protein, albumin, protein electrophoresis with immunofixation and light chains in serum and urine. Quantitative: Immunoglobulin G, M und A, Quick’s test, partial thromboplastin time (PTT), N-terminal pro-brain natriuretic peptide (NT-pro-BNP), troponin

– Bone marrow puncture

– Bone marrow histology:
Evidence/exclusion of lymphoplasmacytic lymphoma
– Bone marrow cytology and flow cytometry

• Additional diagnostic work-up

– Genetic testing

Possibly cytogenetic testing, e.g., del (17p13), t(11;14) (in suspected malignant plasma cell disorder), possibly molecular genetic testing (MYD88 mutations status)

– Imaging

Depending on the suspected diagnosis: ultrasonography, computed tomography (CT) of the neck, chest, and abdomen, low-dose CT, magnetic resonance imaging (MRI)

– Other possible additional investigations

– Lumbar puncture in suspected meningitis
– Fat tissue aspiration, rectal aspiration, or Congo red stain on bone marrow in suspected amyloidosis
– Cryoglobulins, Coombs test (cold agglutinin)
– Myelin-associated glycoproteins (MAG) antibodies (polyneuropathy)
– Hepatitis C in type II cryoglobulinemia
– Endoscopic examination in suspected hyperviscosity syndrome

TABLE 2

Relevant therapeutic regimens in Waldenström's macroglobulinemia

Therapeutic regimen (study design)	ORR (≥ PR) in %	Median survival (in months)	Approval status in WM	Comment
R-CHOP (27) (phase III)	95 (NR)	NA	Cyclophosphamide: NHL Vincristine: NHL Prednisone: NHL Doxorubicin: not approved Rituximab: not approved	Both regimens effective, cave: neurotoxicity of vincristine in R-CHOP regimen, PFS with RB significantly superior in a subgroup analysis compared with R-CHOP (69.5 vs. 28.1 months)
R-bendamustine (27) (phase III)	95 (NR)	NA	Bendamustine: relapsed indolent lymphoma following relapse on rituximab or rituximab-containing treatment Rituximab: not approved	Cave: opportunistic infections under and following bendamustine therapy
DRC (28) (phase II)	83 (74)	95	Cyclophosphamide: NHL Dexamethasone: NHL Rituximab: not approved	Response rates and time to response less than with RB or R-CHOP, but lower toxicity and the option of oral (D and C) and subcutaneous (R) administration. Preferred in older patients and patients without high therapy pressure
FCR (30) (phase II)	79 (74)	69	Fludarabine: not approved Cyclophosphamide: NHL Rituximab: not approved	In part pronounced hemotoxicity, cave: infections, not prior to possibly planned autologous stem cell transplantation (stem cell-toxic)
Bortezomib-R (31) (phase II)	89 (66)	96% After 12 months	Bortezomib: not approved Rituximab: not approved	Rapid efficacy, effective, particularly in the case of high IgM levels; subcutaneous administration reduces neurotoxicity
Ibrutinib (14) (phase II)	91 (73)	95% After 24 months	WM, CLL*, MCL*	Most active single substance in WM. Study conducted in relapsed patients, approved as first-line in patients not eligible for chemotherapy as well as in relapse, daily administration required until progress. ADE: atrial fibrillation, bleeding

*Attention needs to be paid to current approval status. Note: The studies to date have almost all been single-arm with low patient numbers, making them only of limited significance as a basis for evidence-based treatment decisions. Therefore, as far as possible, all patients should be treated in the context of clinical studies. The European Consortium for Waldenström's Macroglobulinemia (ECWM; www.ecwm.eu), together with the German Lymphoma Alliance (GLA), offers new treatment studies especially for patients with WM.

B, bendamustine; C, cyclophosphamide; D, dexamethasone; F, fludarabine; H, doxorubicin; O, vincristine; P, prednisolone; R, rituximab; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; WM, Waldenström's macroglobulinemia; NA, not achieved; NR, not reported; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; ADE, adverse drug effects

IgM myeloma

IgM multiple myeloma (IgM MM) is responsible for 1% of all MM and is often overlooked due to its rarity, since one primarily thinks of WM. The prognosis for IgM myeloma is similar to that of non-IgM myeloma. Genetically, IgM myelomas are in part defined by a t(11;14) translocation, which is not typically found in WM (23). Conversely, an *MYD88* mutation, which is a characteristic genetic aberration in WM, is not found in IgM MM, meaning that genetic tests can support the correct diagnosis in clinically inconclusive cases between these two entities. Since the treatment principles differ, this is of great importance to patients. Furthermore, a flow-cytometry marker profile can help differentiate between the two entities. Clinically, the presence of osteolysis should prompt suspicion of IgM myeloma (24) (Table 1). In addition to the detection of myeloma-related end-organ damage (CRAB criteria), the detection of myeloma-defining events (MDE) should also be taken into consideration in the diagnosis of all MM subtypes as of recently (25).

Diagnostic work-up of monoclonal IgM gammopathy

According to the above-mentioned differential diagnoses and in addition to taking a patient history, a thorough clinical investigation (lymphadenopathy, hepatosplenomegaly, macroglossia, polyneuropathy, periorbital bleeding) should be carried out if monoclonal gammopathy is present. Attention should be paid to identifying signs of amyloidosis, i.e. heart failure, orthostatic dysregulation and dizziness, carpal tunnel syndrome, persistent hoarseness, chronic diarrhea, and the presence of nephrotic syndrome. Bone pain can be a sign of myeloma. Patients in whom monoclonal gammopathy is detected undergo bone marrow puncture in order to initiate further diagnostic investigations on the basis of bone marrow histology and cytology, including flow-cytometry (Box 2).

Treatment

IgM MGUS

Patients with IgM MGUS do not usually require treatment. However, patients should be regularly monitored.

FIGURE

Treatment algorithms for first-line treatment of patients with Waldenström's macroglobulinemia (modified from [26]).

*1 Ofatumumab in the case of rituximab intolerance.

*2 The choice of individual regimen depends, among other things, on the presence of comorbidity/age, as well as the need for rapid disease control. In patients with an aggressive course, stem cell-toxic substances, such as nucleosides (cladribine/fludarabine) and oral alkylating agents such as chlorambucil, should be avoided in view of the potential need for autologous stem cell transplantation in the further course.

CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; WM, Waldenström's macroglobulinemia

If IgM MGUS is present, an initial follow-up should be carried out after 6 months and annually thereafter if results are stable (6).

Waldenström's macroglobulinemia

In general, patients with asymptomatic WM (smoldering WM) undergo a watch-and-wait strategy. If lymphoma- and IgM-related symptoms, as well as lymphoma-related cytopenia/anemia occur and IgM levels rapidly rise above 5g/dl, treatment based on the patient's general condition and co-morbidities is indicated.

First-line treatment – The treatment of choice in WM remains combined rituximab and chemotherapy (Table 2) (26). A combination of the monoclonal CD20 antibody rituximab (alternatively ofatumumab in the case of intolerance) plus bendamustine (BR) or cyclophosphamide and dexamethasone (DRC) is primarily recommended. The data for BR are based on a subgroup analysis of a randomized phase III trial in which rituximab/bendamustine statistically significantly increased progression-free survival (PFS) with overall good tolerability in a total of 40 WM patients compared with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (69.5 months versus 31.2 months, $p < 0.0001$). Response rates of over 90% were achieved in both arms. With overall response rates of 83%, the DRC regimen is somewhat slow in terms of response, but has the advantage that it does not require intravenous administration and that it causes virtually no grade III/IV hematological toxicities in

first-line treatment (28, 29). Although nucleoside-containing regimens, such as FCR (fludarabine, cyclophosphamide, and rituximab) are effective, some have very high side-effect profiles, often involving pronounced and long-term myelotoxicity. Total response rates of 79% were reported in this collective (30). Ibrutinib is approved as the first-line treatment in patients not suited to rituximab/chemotherapy, as well as in all relapsed patients. This approval is based on study data showing a total response rate under ibrutinib therapy of 91% in patients with relapsed/refractory disease. Ibrutinib is generally effective within 8 weeks. A disadvantage, however, is that the substance needs to be administered daily and is significantly less effective in particular in genotype 3 (*MYD88* wild-type/*CXCR4* wild-type). Furthermore, the substance can cause atrial fibrillation and a propensity for bleeding (14). Combining the protease inhibitor bortezomib with rituximab represents a further treatment option. This combination showed high overall response rates of 89% in several phase II studies. The clinically relevant problem of induced neuropathies known under protease inhibitors could be reduced by once-weekly subcutaneous administration (31).

Rituximab monotherapy represents a treatment option in some patients with comorbidities and poor general condition, with remission rates of 66% seen (32). However, the risk of an IgM flare, a critical increase in IgM, needs to be taken into consideration. The Figure shows the treatment algorithm for the first-line treatment of WM.

Relapse management – At present, rituximab chemotherapy is the treatment of choice for the management of relapse. If the duration of remission is longer than 12 months, first-line therapy can be repeated; alternatively, a switch to a non-cross-resistant rituximab chemotherapy can be attempted (*eFigure, Table 2*) (26, 33–35). Ibrutinib, as described in first-line treatment, is a newly (July 2015) approved medication for recurrent WM (14). Recent studies show that ibrutinib is also a treatment option in patients refractory to prior treatment with rituximab (36). However, it should be noted at this point that none of new treatment options currently available are curative. A comprehensive overview of the latest treatment options is provided in the summary of the 8th International Workshop on Waldenström's Macroglobulinemia (34).

IgM myeloma

The treatment of IgM myeloma is similar to that of non-IgM myeloma. The interested reader is referred to the review article “The Diagnosis and Treatment of Multiple Myeloma” recently published in *Deutsches Ärzteblatt International* (37).

IgM-related disorders

Cold agglutinin disease generally responds inadequately to corticosteroids or splenectomy. If therapy is required, the current treatment of choice is rituximab, primarily as a monotherapy or alternatively in combination with chemotherapy (e.g., fludarabine) (38). In the case of rituximab-refractory, transfusion-dependent patients, eculizumab may be considered as an option in some cases. This is a monoclonal antibody that binds to the complement protein C5, thus inhibiting the formation of the terminal complement complex (22, 38). The treatment of IgM-related neuropathy depends to a large extent on the degree of impairment to the patient's quality of life. If symptoms are limited, a wait-and-see strategy is recommended. In the case of progressive polyneuropathy, rituximab monotherapy is the treatment of choice in many institutions; in the case of concomitant WM or higher-grade polyneuropathy, rituximab and chemotherapy, such as rituximab plus bendamustine are additionally recommended (19).

Conflict of interests

Prof. Buske has received fees for consulting services, lectures, funding for a research project initiated by him, and reimbursement of travel and accommodation expenses from Janssen and Roche. He has also received reimbursement from Roche and Abbvie for participation fees for congresses. Dr. Grunenberg declares that no conflict of interest exists.

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KEY MESSAGES

- The most common diagnosis in IgM monoclonal gammopathy is IgM MGUS, which does not require treatment per se. However, there is a risk of progression to malignant disease, hence regular laboratory tests are recommended.
- Waldenström's macroglobulinemia is rare (3.8 per one million persons in the US) and is defined by the detection of monoclonal IgM in serum and the histological finding of at least 10% bone marrow infiltration by clonal lymphoplasmacytic cells.
- As a rule, only symptomatic Waldenström's macroglobulinemia is treated. Symptoms can vary greatly and manifest as hyperviscosity syndrome, anemia, and/or autoimmune phenomena.
- The standard therapy for Waldenström's macroglobulinemia is rituximab and chemotherapy. Ibrutinib represents an effective chemotherapy-free treatment. It is approved as first-line treatment in patients not suited to a first-line rituximab and chemotherapy regimen, as well as in all relapsed patients.
- The recommended treatment regimen depends heavily on the patient's general condition.

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Supplementary material

eReferences:
www.aerzteblatt-international.de/ref4417

eTables, eFigures:
www.aerzteblatt-international.de/17m0745

Supplementary material to:

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eTABLE 1

Mayo Clinic risk model to estimate the risk of progression (from [7])

Risk factors	Number of risk factors	Risk group	Risk of progression within 20 years
Non-IgG MGUS	0	Low	5%
Monoclonal protein ≥ 15 g/L	1	Low-intermediate	21%
Abnormal light chain ratio	2	High-intermediate	37%
	3	High	58%

MGUS, monoclonal gammopathy of undetermined significance

eTABLE 2

Concomitant symptoms of Waldenström's macroglobulinemia (modified from [11, 12])

Concomitant symptoms caused by lymphoma	IgM-induced concomitant symptoms
Anemia (30–40%)	Hyperviscosity syndrome (35%)
Thrombopenia (16%)	Amyloidosis (≈ 3%)
Leukopenia (4%)	Cryoglobulinemia (with vasculitis) (20%)
Lymphadenopathy (20–25%)	Hemolysis due to cold hemagglutinins (10%)
Hepatosplenomegaly (20–25%)	Polyneuropathy (up to 40%)
B symptoms (fever, night sweats, unintentional weight loss >10% of body weight in 6 months)	

eFIGURE

Treatment algorithms for patients with relapsed Waldenström's macroglobulinemia (WM) (modified from [26])

*¹ High-dose therapy followed by ASCT in chemosensitive relapsed WM is an important treatment option for patients in good general condition, particularly in more clinically aggressive cases.

*² Allogeneic stem cell transplantation after myeloablative conditioning or reduced intensity conditioning should only be performed in highly selected cases and preferably in studies.