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Waldenström macroglobulinemia: diagnosis and treatment

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Abstract

Waldenström macroglobulinemia (WM), according to the 2017 World Health Organization classification, is defined as the co-occurrence of lymphoplasmacytic lymphoma involving the bone marrow with monoclonal gammopathy of the IgM class regardless of the concentration of monoclonal protein. It is a rare lymphoproliferative disease with distinctive clinical features. Diagnostic characteristics in WM have changed significantly with the discovery of two molecular markers: MYD88 and CXCR4. The mutational status of these markers both affects clinical presentation and has shown therapeutic implications. The choice of treatment in WM is closely dependent on the patient's age, risk of treatment-related neuropathy, and risk of immunosuppression or secondary malignancies. The therapeutic landscape has broadened in recent years, and the approvals of ibrutinib and zanubrutinib represent a significant step forward toward better management of the disease.

Key words: Waldenström macroglobulinemia, lymphoplasmacytic lymphoma, monoclonal immunoglobulin M (IgM), BTK inhibitor, ibutrinib, zanubrutinib, rituximab

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Introduction

Lymphoplasmacytic lymphoma (LPL) is a malignancy composed of small B cells, plasmacytoid lymphocytes and plasma cells. It usually affects the bone marrow, and sometimes the lymph nodes and spleen, and at the same time does not meet the criteria for the diagnosis of another small B cell neoplasm, which may also be characterized by plasmacytic cell differentiation [1]. Most cases of LPL are accompanied by the production of monoclonal IgM serum protein, which meets the criteria for Waldenström's macroglobulinemia (WM), and only less than 5% of patients with LPL IgA, IgG monoclonal proteins or non-secretory LPL is detected [2, 3]. Family history of LPL or WM was confirmed in 4.3% of patients, and familial occurrence is associated with a worse prognosis [4].

Diagnosis

The diagnosis of WM requires the presence of an IgM monoclonal protein in serum electrophoresis or immunofixation, regardless of its concentration and LPL infiltration in the bone marrow [2, 3]. The infiltration may be diffuse, interstitial or nodular, usually intertrabecular. An increased percentage of mast cells, usually located around lymphocytic infiltrates, is also characteristic. Bone marrow examination must be supported by immunophenotyping by flow cytometry and/or immunohistochemistry. Genetic tests are helpful in the diagnosis of WM, and in particular in the differentiation from other lymphomas. The *MYD88* L265P mutation occurs in over 90% of patients with WM, and the *CXCR4* gene mutation in 30–40% of patients. Del 6q21-25 (BLIMP-1) is

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found in 40–50% of patients with WM, while is very rarely seen in other lymphoid malignancies. In patients with WM, no correlation was found between the concentration of IgM protein and the degree of bone marrow infiltration by lymphoma cells. When determining the IgM concentration, it should be remembered that its value may be influenced by the presence of cold agglutinins or cryoglobulins in the patient's serum, therefore appropriate tests should be performed up-front at the time of diagnosis. Bence-Jones protein is present in the urine of patients with WM, but its daily excretion usually does not exceed 1 g, therefore urine electrophoresis is not routinely recommended in most patients with WM. Determination of serum light chain concentration, which is obligatory in patients with PCM, is not necessary for the routine diagnosis of WM. Leleu et al. [5] demonstrated the influence of serum light chain concentration in WM patients on the time of disease progression and the time to respond, but their prognostic role requires further investigation.

Clinical manifestation

Two main categories of MW symptoms can be distinguished — symptoms related to the bone marrow and other organs infiltration by lymphoma cells and/or the presence of a monoclonal IgM class protein (Table 1) [6, 7]. Cytopenias, particularly anaemia, are among the more common symptoms of WM; splenomegaly and/or hepatomegaly and lymphadenopathy are found in about 20% of patients. Patients with an IgM concentration above 50 g/L are at high risk of developing hyperviscosity syndrome (HVS). In some patients with WM, the presence of IgM monoclonal protein may manifest as neuropathy, cryoglobulinemia, skin rash (Schnitzler syndrome), cold agglutinin disease (CAD) or amyloidosis [5, 6]. In very few cases of WM, lymphoma cell infiltration of the lungs (diffuse or nodular infiltrates, pleural effusion) is observed, which may clinically manifest as cough, shortness of breath or chest pain. Intestinal infiltrates may be the cause of malabsorption, manifesting as diarrhoea or bleeding, and infiltrations in the central nervous system are referred to as Bing-Neel syndrome. This syndrome is characterized by headaches and dizziness, confusion, ataxia and diplopia, and even coma. It is usually associated with long-term HVS, which causes increased vascular wall permeability, and facilitates the formation of perivascular infiltrates of lymphoma cells [5, 6].

Table 1. Clinical symptoms of Waldenström's macroglobulinemia (based on [6, 7])

Cause	Symptoms
Infiltration by lymphoma cells	• Cytopenias • General symptoms (fever, night sweats, weight loss) • Enlarged lymph nodes • Splenomegaly, hepatomegaly
IgM monoclonal protein	• Hyperviscosity syndrome • Cryoglobulinemia • Cold agglutinin disease • Neuropathy • Amyloidosis

Classification of Waldenström's macroglobulinemia and diseases associated with the presence of monoclonal IgM protein

Patients with plasma cell dyscrasias with the presence of monoclonal IgM protein could be divided into a few subgroups, depending on the presence or absence of specific clinical symptoms: patients with WM symptoms, asymptomatic patients, patients with IgM-related disorders and patients with monoclonal gammopathy of undetermined significance (MGUS IgM) (Table 2). The latter is diagnosed in asymptomatic patients with an IgM protein concentration below 30 g/L and LPL infiltration assessed by bone marrow biopsy as below 10%, normal haemoglobin concentration and normal platelet count. Asymptomatic WM is defined as LPL infiltration in trephine biopsy of at least 10% and/or the presence of IgM monoclonal protein at a concentration of at least 30 g/L, but without the coexistence of clinical signs and symptoms of organ damage characteristic for WM. Some patients may have clinical symptoms due to the presence of abnormal IgM protein and its biological properties, but with no other symptoms related to lymphoma cell infiltration. Such patients are diagnosed with IgM-related disorders, which most often manifest as peripheral neuropathies, cryoglobulinemia, CAD or primary amyloidosis. The IgM protein is usually found in low concentrations in these patients and is produced by a small clone of B lymphocytes/plasma cells, sometimes undetectable in bone marrow morphology [6, 7].

The International Prognostic Scoring System for Waldenström macroglobulinemia

The International Prognostic Scoring System for Waldenström macroglobulinemia is a widely

Table 2. Classification of Waldenström's macroglobulinemia (WM) and IgM-related disorders (acc. to [3])

Criterion	MGUS IgM	Asymptomatic WM	Symptomatic WM	IgM-related disorders
Monoclonal IgM protein	< 30 g/L	≥ 30 g/L	+	+
Bone marrow infiltration	< 10%	≥ 10%	≥ 10%	±*
Symptoms associated with lymphoma infiltrates	–	–	+	–
IgM related symptoms	–	–	±	+

*B cell clone detected by flow cytometry or polymerase chain reaction in the absence of morphological features of bone marrow infiltration by lymphoma cells; MGUS IgM — monoclonal gammopathy of undetermined significance

Table 3. Stratification of patients according to the International Prognostic Scoring System for Waldenström macroglobulinemia (acc. to [8])

Risk group	Risk factors*	Percentage of patients
Low risk	0–1 factors and age ≤ 65 years	87%
Intermediate risk	2 factors or age > 65 years	68%
High risk	3–5 factors	36%

*IPSSWM risk factors: age > 65 years, haemoglobin < 11.5 g/dL, platelet count < 100 g/L, beta$_2$-microglobulin > 3 mg/L, IgM > 70 g/L

recognized prognostic indicator for WM, which includes five unfavourable risk factors, such as age over 65 years, haemoglobin concentration less than or equal to 11.5 g/dL, platelet count less than or equal to 100 G/L, a serum beta$_2$-microglobulin concentration higher than 3 mg/L, and an IgM monoclonal protein concentration higher than 70 g/L. Depending on the number of the above-mentioned factors, low-, intermediate-, and high-risk groups were distinguished, and the probability of 5-year overall survival (OS) was estimated [8] (Table 3). The International Prognostic Scoring System should not be used to make decisions about initiating systemic treatment.

Pathogenesis

This malignancy originates from a clonal B cell that has undergone a process of somatic hypermutation in the germinal centres of the lymphoid follicle, and possibly been in contact with the antigen, but whose development was arrested before final differentiation into a plasma cell. The analysis of somatic mutations in the genes encoding variable regions of the immunoglobulin heavy and light chain indicates that WM originates from an immune memory B cell expressing IgM (IgM+) and/or IgM and IgD (IgM+/IgD+), which in the process of differentiation is not able to enter the so-called stage of synthesized antibodies class change. Del 6q21-25 was found in 40–50% of patients with WM. In this region, the gene *BLIMP-1* (B lymphocyte-induced maturation protein 1; *PRDM1*) and *TNFAIP3* (tumour necrosis factor α-induced protein 3; A20) were identified, among others. The *PRDM1* gene encodes a transcription factor that inhibits the activity of genes involved in cell proliferation and differentiation of B lymphocytes into plasma cells. In turn, *TNFAIP3* is a suppressor gene, the inactivation of which leads to the constitutive activation of the nuclear transcription factor kappa B (NF-κB), which plays a key role in the pathogenesis of WM [9].

Mutations in the *MYD88* gene

The MYD88 (myeloid differentiation primary response 88) protein is an adapter protein that interacts with Toll-like receptors and interleukins (interleukin [IL] 1) and dimerizes upon receptor activation. MYD88 dimerization provides a scaffold for the recruitment of other proteins to the myddosome complex, which triggers the signalling leading to the activation of NF-κB [10]. The components of the myddosome complex that triggers the activation of NF-κB also include interleukin-1 receptor-associated kinase 1/4 (IRAK1/IRAK4) and Bruton tyrosine kinase (BTK) [11]. Uptake and activation of IRAK and BTK molecules can be blocked by suppression or inhibition of MYD88 function, leading to apoptosis of MYD88-mutant WM cells. Mutant MYD88 can also increase the transcription of the protein tyrosine kinase HCK (SRC family non-receptor tyrosine kinase) and activate HCK via IL-6. Activated HCK triggers

survival-promoting signalling in MYD88-mutant WM cells via BTK, phosphatidylinositol 3-kinase-AKT (PI3K/AKT), and mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MAPK/ERK1/2) [12]. The MYD88 mutation also activates the protein tyrosine kinase SYK, which is part of the B-cell receptor (BCR) signal transduction pathway. Activated SYK triggers signal transducer and activator of transcription-3 (STAT3) and survival-promoting AKT signalling, highlighting the possible use of SYK inhibitors in the treatment of WM [13]. Mutant MYD88 can drive several survival-promoting cascades in WM cells that lead to the activation of NF-κB, AKT, ERK and STAT3 [14]. The *MYD88* L265P mutation is present in more than 90% of WM patients and may promote lymphoma development by stimulating intracellular signalling pathways involving BTK and constitutive NF-κB activation. The *MYD88* L265P mutation has not been observed in patients with multiple myeloma, but it has been found in approximately 7% of patients with marginal zone lymphoma (MZL).

Mutations in the *CXCR4* gene

The C-X-C chemokine receptor type 4 (CXCR4) is a G protein-coupled receptor that, together with its ligand CXCL12/SDF-1 (stromal cell-derived factor 1, chemokine 12), plays an important role in lymphopoiesis [15]. The SDF1/CXCR4 pathway induces the activation of several pathways, including RAS, AKT and NF-κB, and interacts with the BCR pathway [15–17]. Somatic mutations involving the C-terminal domain of CXCR4 occur in 30–40% of patients with WM, with the *CXCR4* C1013G mutation being the most common and occurring in 7% of patients. They are almost always associated with MYD88 mutations, but some patients with the MYD88 mutation also have CXCR4 mutations [15, 18, 19]. CXCR4 mutations are predominantly found in WM, although cases of MZL and diffuse large B-cell lymphoma with mutations in this gene have been reported. More than 40 "nonsense" and frameshift mutations of the C-terminal domain of CXCR4 have been described in WM [17, 20]. Mutations in the C-terminal domain of CXCR4 lead to loss of regulatory serines and promote continuous CXCL12-driven activation of AKT and ERK pathways, which is reflected in the progression and spread of WM *in vivo* mouse experimental models [12, 20, 21]. Despite the autonomous cell survival-promoting signalling associated with the CXCR4 mutation, inhibition of MYD88 causes apoptosis of WM cells independently of the *CXCR4* mutation, which is consistent with the hypothesis that the MYD88 mutation plays a fundamental role in the survival-promoting signalling in WM cells [12]. Unlike the MYD88 mutation, the CXCR4 mutation is subclonal; different CXCR4 mutations may be present in different WM cell clones. These results, together with the low incidence of CXCR4 mutations in IgM MGUS, suggest that the CXCR4 mutation follows the MYD88 mutation [22]. It has been shown that the type of mutation in the *MYD88* and *CXCR4* genes has clinical implications and affects the response to ibrutinib treatment [23].

Indications for treatment initiation

Indications for treatment initiation are presented in Table 4. If the patient does not meet the above criteria, and only the results of laboratory tests indicate slight abnormalities (such as a slight decrease in haemoglobin [Hb] concentration, but > 10 g/dL, or a moderate increase in IgM concentration), regular follow-up is recommended [24, 25]. It should be emphasized that in the previous recommendations, the level of IgM, if not associa-

Table 4. Indications for treatment initiation in patients with Waldenström's macroglobulinemia (WM) (sources [23, 24])

Clinical indications	Laboratory indications
• Disease-related systemic symptoms, including fever of unknown origin > 38°C for more than 2 weeks and/or night sweats and/or weight loss, i.e. loss of ≥ 10% of body weight in ≤ 6 months, and/or fatigue • Symptoms of hyperviscosity syndrome • Symptomatic or severely enlarged lymph nodes (maximum dimension ≥ 5 cm) • Symptomatic hepatomegaly and/or splenomegaly • Symptomatic organomegaly and/or symptomatic organ or tissue infiltration • Symptomatic neuropathy due to WM	• Symptomatic cryoglobulinemia • Cold agglutinin disease • Immune haemolytic anaemia and/or immune thrombocytopenia • WM-related nephropathy • WM-related amyloidosis • Hb level ≤ 10 g/dL • PLT count < 100 G/L • IgM concentration > 60 g/L

Hb — haemoglobin; PLT — platelets

ted with clinical symptoms, was not an indication for treatment initiation. According to the 2019 European School of Medical Oncology (ESMO) recommendations, the IgM concentration above 60 g/L correlates with the risk of rapid development of HVS, which is why it was considered a sufficient parameter for therapy commencing [26]. Patients with asymptomatic WM should be followed every 2–3 months in the first year from diagnosis to determine the dynamics of the disease, and then, if the disease is stable, the intervals between follow-up visits may be longer. [9, 25, 26].

Treatment

First-line treatment

The choice of first-line treatment takes into account the potential qualification for autologous hematopoietic stem cell transplantation (auto-HSCT), clinical picture including cytopenias, symptoms related to the presence of IgM protein and comorbidities [9, 25–27]. If, mainly due to the age and patient's general condition, auto-HSCT is planned in the further stages of therapy, the continuous use of purine base analogues or chlorambucil is not recommended due to potential difficulties in obtaining stem cells.

The recommended first-line treatment regimens according to the 10th International Workshop on Waldenström's Macroglobulinemia (IWWM-10) and ESMO are DRC (dexamethasone, rituximab, cyclophosphamide), BDR (bortezomib, dexamethasone, rituximab) or BR (bendamustine, rituximab). The R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) is no longer recommended as the first-choice treatment [25–27]. Treatment BR, BDR, and DRC regimens are presented in Table 5. In patients with mild symptoms of WM or IgM-associated disorder, rituximab monotherapy may be used. Rituximab and bortezomib are not approved for the treatment of WM, and bendamustine is not approved for first-line treatment. Apart from ibrutinib and zanubrutinib, particular drugs are available in the chemotherapy catalogue of the National Health Fund (NFZ), except for bendamustine available in the first-line treatment in the case of contraindications to treatment with an anthracycline [28].

Treatment of refractory or relapsing disease

ESMO recommends ibrutinib monotherapy in patients refractory to previous treatment containing rituximab or in patients with WM relapse in less than 1 year [29]. For patients who have responded to treatment for 1 to 3 years, ESMO also recommends ibrutinib or immunochemotherapy regimens that contain different drugs than those used previously. On the other hand, in patients with WM recurrence after 3 years, the previously used regimen of immunochemotherapy can be repeated or an alternative regimen or ibrutinib can be used [26].

New treatment options are necessary for the treatment of patients with relapse [30, 31]. Ibrutinib, the first-in-class BTK inhibitor, has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with WM. Targeting BTK in WM has changed the treatment landscape; in a pivotal phase II study, 63 patients with symptomatic relapse received oral ibrutinib 420 mg daily until progressive disease (PD) or unacceptable toxicity. Overall response rates (ORR) were achieved in 90.5% of patients, including complete responses (CR) in 73% of patients [32]. In later analyses, it was noted that the responses differed depending on the MYD88 and CXCR4 mutations, with the highest response rates in the group of MYD88^{mut}/CXCR4^{wt} patients, intermediate in MYD88^{mut}/CXCR4^{mut}, and the lowest in MYD88^{wt}/CXCR4^{wt} cases [33]. Second-generation BTK inhibitors are characterized by a better selectivity of kinase inhibition, which results in a reduction of side effects and may increase the effectiveness of therapy. Zanubrutinib, a second-generation BTK inhibitor, demonstrated deeper responses in phase III randomized study comparing its efficacy directly to ibrutinib monotherapy, with no differences in progression-free survival (PFS) or OS. Twenty-nine (28%) patients treated with zanubrutinib and 19 (19%) patients treated with ibrutinib achieved a very good partial response (VGPR) ($p = 0.09$). At 18 months, 84% and 85% of patients treated with ibrutinib and zanubrutinib had not developed PD. Cardiac and haemorrhagic events, but also diarrhoea, oedema, muscle spasms and pneumonia, as well as adverse events leading to treatment discontinuation, occurred less frequently in patients receiving zanubrutinib. Efficacy was also observed in the group of patients without the MYD88 mutation [34]. This subgroup consisted of 28 patients (23 relapsed/refractory; 5 treatment-naïve), including 26 with centrally confirmed MYD88 mutation negative and 2 with unknown MYD88 mutation status. With a median follow-up of 17.9 months, 7 of 26 patients (27%) achieved VGPR and 50% achieved a major response (PR or better). At 18 months, the estimated PFS and OS rates were 68%

Table 5. Treatment regimens used in the therapy of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia

Regimen and drugs	Dosage and route of administration	Day of use	Comments
BR			4 cycles repeated every 4 weeks (reducing the bendamustine dose should be considered in elderly patients and patients with renal failure)
Bendamustine	90 mg/m^2 iv	1st, 2nd	
Rituximab	375 mg/m^2 iv	1st	
DRC			6 cycles repeated every 3 weeks
Dexamethasone	20 mg iv	1st	
Rituximab	375 mg/m^2 iv	1st	
Cyclophosphamide	100 mg/m^2 po 2 ×/day	1st–5th	
BDR			4 cycles repeated every 3 weeks
Bortezomib	1.3 mg/m^2 sc or possibly iv	1st, 4th, 8th, 11th	
Dexamethasone	40 mg iv	1st, 4th, 8th, 11th	
Rituximab	375 mg/m^2 iv	11th	
FR			6 cycles repeated every 4 weeks
Fludarabine	25 mg/m^2 iv	1st–5th	
Rituximab	375 mg/m^2 iv	1st	
Ibrutinib ± rituximab			
Ibrutinib	420 mg po	1 ×/day until disease progression or unacceptable toxicity	
Rituximab	375 mg/m^2 iv	1st, 8th, 15th, 22th (1st and 5th months)	
Zanubrutinib			
Zanubrutinib	2 × 160 mg po	2 ×/day until disease progression or unacceptable toxicity	
Rituximab			The cycle can be repeated after 12 weeks
Rituximab	375 mg/m^2 iv	1st, 8th, 15th, 22th	
VR			6 cycles repeated every 4 weeks
Bortezomib	1.6 mg/m^2 sc or possibly iv	1st, 8th, 15th	
Rituximab	375 mg/m^2 iv	1st, 8 th, 15th, 22th (cycle 1st and 4th)	

iv — intravenous; po — per os (orally); sc — subcutaneous

and 88%, respectively. Zanubrutinib is approved by the FDA and EMA for the treatment of adult patients with MW who have received at least one prior treatment, or for the first-line treatment of patients not eligible for chemoimmunotherapy. In a randomized phase II study, acalabrutinib was evaluated in a group of 122 patients with previously untreated WM (n = 14) or with relapsed WM (n = = 106). After a median follow-up of 27.4 months, the response rate was 93% for first-line treatment and 93% for relapsed/refractory patients [35]. A lower incidence of atrial fibrillation and bleeding complications were observed compared to the historical ibrutinib group.

The effectiveness of BTK inhibitors in combination therapy is also being analysed. In the case of therapy with ibrutinib and rituximab, the 30-month PFS rate was 82% compared to 28% in the group receiving a placebo with rituximab [36]. The superiority of the ibrutinib + rituximab group over the placebo + rituximab group was independent of MYD88 or CXCR4 genotype. According to the recommendations of the IWWM-10 expert panel, polymerase chain reaction (PCR) tests to assess the MYD88 and L265P mutations should be performed when ibrutinib is used, and ibrutinib monotherapy should not be used in patients without the MYD88 mutation. The IWWM-10 experts also noted that there is insufficient

data to recommend ibrutinib with rituximab instead of ibrutinib monotherapy [37].

Assessment of treatment response

There are the following categories of treatment response distinguished in patients with MW: 1) CR, in which monoclonal IgM protein remains undetectable in immunofixation, IgM concentration is normal, lymph nodes and spleen are not enlarged, and the bone marrow morphology in bone marrow aspiration biopsy and trephine biopsy is normal; 2) VGPR, occurring when the IgM concentration is reduced by at least 90% and the lymph nodes and spleen are much less enlarged; 3) PR, which defines a state in which the decrease in IgM concentration is greater than or equal to 50% but less than 90%, while the dimensions of the lymph nodes and spleen have decreased by more than 50%; 4) minor response (MR), characterized by a decrease in IgM concentration by at least 25% but less than 50%. Stable disease (SD) is defined as a decrease in IgM levels of less than 25% or an increase of less than 25% and no progression of lymphadenopathy and splenomegaly. On the other hand, an increase in IgM concentration by at least 25% and progression of clinical symptoms indicate PD [28].

Summary

The assessment of the MYD88 and CXCR4 mutations significantly improved the diagnostic capabilities in patients with MW. The therapy of patients with MW has significantly improved in recent years, and more and more targeted therapies are used in real-world practice and clinical trials. The registration of BTK inhibitors — ibrutinib and zanubrutinib — is a breakthrough in the treatment of patients with refractory and relapsing WM, and in the future it will be more and more often used from the first-line of therapy.

Conflict of interest

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