Waldenström macroglobulinemia—definition, symptoms, and treatment
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ABSTRACT
Waldenström macroglobulinemia (WM) is a low-grade lymphoplasmacytic lymphoma of mature IgM⁺ B–lymphocytes that remains incurable despite recent practice–altering therapeutic advances and refinements in patient care. Defining features of WM include symptoms that can either be attributed to the extent and site of tissue infiltration by tumor cells or the magnitude and immunological specificity of the monoclonal serum IgM (paraprotein). Current guidelines for the therapeutic stratification of patients with newly diagnosed WM recommend BR (bendamustin–rituximab) for bulky and/or symptomatic disease. DRC (dexamethasone–rituximab–cyclophosphamide) is a good treatment option for relapsed or refractory WM. Ibrutinib—a small–drug inhibitor of Bruton tyrosine kinase, approved for WM treatment in the United States and Europe in 2015—is particularly effective for tumors that harbor the hallmark MYD88L265P mutation. Plasma exchange is indicated in patients with IgM-dependent hyperviscosity syndrome. The potential development of novel drugs and combination regimens generates promise that the future of patients with WM is bright.

Keywords: lymphoplasmacytic lymphoma, mature IgM⁺ B–lymphocytes, serum paraprotein, Bruton tyrosine kinase, hyperviscosity syndrome

ABBREVIATIONS
ASCT autologous stem cell transplantation
CLL chronic lymphocytic leukemia
HVS hyperviscosity syndrome
Ig immunoglobulin
LPL lymphoplasmacytic lymphoma
LPC(s) lymphoplasmacytic cell(s)
MCL mantle cell lymphoma
MGUS monoclonal gammopathy of undetermined significance
MM multiple myeloma
mIgM monoclonal immunoglobulin M, IgM paraprotein, IgM spike

WM—BRIEF OVERVIEW OF CLINICAL ASPECTS
Waldenström macroglobulinemia (WM) is a neoplasm of mature IgM–expressing B–lymphocytes that is characterized by the occurrence of a monoclonal IgM (mIgM) paraprotein in the blood serum and the infiltration of the hematopoietic bone marrow with malignant lymphoplasmacytic cells. The symptoms of patients with WM can be attributed to the extent and sites of tissue infiltration with tumor cells as well as the magnitude and immunological specificity of the
paraprotein. WM remains incurable despite the development of new therapeutic options. Owing in large measure to low incidence, indolent clinical course and good long-term control with proper clinical management, WM has not been investigated as extensively as other B–lineage neoplasms. Nonetheless, important advances in our understanding of the natural history of WM have been made recently. This includes the discovery of a specific gain–of–function mutation in the MYD88 adapter protein, MYD88
\[ L265P \]
, which strongly suggests that the tumor is under selective pressure for elevated MYD88 signaling. The hallmark MYD88 mutation also provides an intriguing clue about the cell of origin of WM, which will be the subject of another mini–review in this journal in the not–so–distant future. Following below is a brief account of clinical aspects of WM, focusing on symptoms, diagnosis, and treatment of this rare blood cancer.

**DEFINITION AND CLASSIFICATION**

WM is caused by a lymphoplasmacytic lymphoma (LPL) that involves the bone marrow and is associated with a monoclonal immunoglobulin (Ig) of the M class in the serum. The monoclonal IgM is usually referred to as IgM paraprotein or M spike–or mIgM for short. LPL is a low-grade malignancy of the mature B–lymphocyte lineage that exhibits a cytological spectrum of lymphoplasmacytic differentiation that ranges from small B–cells to fully differentiated plasma cells (PCs). Lying in between is a sizable if not predominant fraction of cells with intermediate features, designated lymphoplasmacytoid or lymphoplasmacytic cells (LPCs). These cells are sometimes referred to as plasmacytoid lymphocytes or plasmacytic lymphocytes. The histopathologic diagnosis of LPL can be challenging, even for an experienced hematopathologist, because it is based in large measure on the exclusion of other small B–cell lymphoid neoplasms. Establishing the diagnosis of WM from lymph node or spleen—rather than from a bone marrow biopsy, which is the case in the great majority of patients—can be particularly difficult. Although LPL is characteristically associated with a mIgM that can be readily detected by serum protein electrophoresis, LPL does not always lead to WM. This is because approximately 5% of LPLs either produce a paraprotein that is not of the M class (instead, it belongs in most cases to the A class or one of the four G subclasses) or produce no Ig at all (i.e., the non–secretory variant). Similarly, although the presence of a serum IgM spike immediately raises suspicion of LPL, this type of lymphoma is not the sole underlying cause for the laboratory finding. Thus, IgM paraproteins can also be produced by marginal zone, mantle cell and other types of B–cell lymphoma with plasmacytic differentiation potential—or, in rare cases, by bona fide plasma cell neoplasms such as IgM plasmacytoma or IgM myeloma. In sum, even though LPL does not always lead to WM and the occurrence of a serum IgM spike is not pathognomonic for the disease, WM is always caused by IgM+ LPL (Fig. 1).

**SYMPTOMS ATTRIBUTABLE TO TUMOR GROWTH**

The great majority of patients with LPL exhibit distinctive clinical features that can be attributed either to tissue infiltration with malignant B–cells (Fig. 2, left) or IgM–dependent changes in serum (hyperviscosity syndrome) and various tissue sites (immunoglobulin deposition disease, autoimmunity; Fig. 2, right). With regard to tissue infiltration by tumor cells, the replacement of the normal hematopoietic bone marrow with WM cells usually leads to a progressive normochromic or normocytic anemia and, to a lesser extent, suppression of other blood cell lineages, which may result for example in thrombocytopenia. Tumor infiltrates in solid tissues may clinically present as organomegalies, including hepato– and spleno–megaly as well as lymphadenopathy. In rare cases, malignant infiltration of the lung (accompanied by
pleural effusion\[^7\], the gastrointestinal tract\[^8\], and the skull (involving the orbitae\[^9\] or generating epidural masses) have been observed. Bing–Neel syndrome—which consists of headache, vertigo, impaired hearing, ataxia, nystagmus, diplopia, and, in terminal stages, coma—is a vicious CNS (central nervous system) complication of WM caused by blood vessel damage, IgM deposition and perivascular lymphoma cell infiltration in the brain and spinal nerves\[^10\]. Malignant vitreitis and conjunctival infiltration are rare ocular manifestations of WM. The syndromic presentation of IgM paraproteinemia and associated clinical features was first recognized by the Swedish doctor of internal medicine, Jan Gösta Waldenström, who published his initial observations in the 1940s. His findings were swiftly embraced by hematologists in other countries and, within a few years, the term Waldenström macroglobulinemia was coined and commonly accepted. Since Waldenström’s landmark report some 75 years ago, we have learned a great deal about the clinical presentations and complications of the disease, including the symptoms attributable to the hallmark IgM monoclonal gammopathy described in the following.

**SYMPTOMS ATTRIBUTABLE TO mIgM**

Under normal conditions, IgM predominantly occurs in serum in pentameric form. Five IgM monomers, each consisting of two \(\kappa\) heavy chains and two \(\lambda\) light chains, are covalently linked by the J or joining chain, resulting in a supramolecular complex that is often schematically depicted as a snow flake or five–leafed shamrock. The pentameric structure of IgM results in a large molecular mass (~970 kilodalton), high avidity to antigen (10 antigen–binding sites), and high potential for complement activation. However, the flip side of these features is poor diffusion properties, low concentration in interstitial fluids, and poor ability to leave the blood stream. In patients with WM, the elevated concentration of monoclonal IgM can lead to serum hyperviscosity, a key distinguishing feature of the disease. Symptoms include bleeding and a multitude of ocular, neurologic, and cardiovascular manifestations\[^11\]. Thanks to an earlier recognition of the disease in recent years, serum hyperviscosity is only observed in a minority of patients at diagnosis\[^12,13\]. As a rule, symptoms of hyperviscosity are rare in patients with IgM levels below 30–40 g/L and serum viscosity values below 4 cP (centipoise). This threshold corresponds to a 2.5–fold increase relative to normal serum viscosity, which is in the neighborhood of 1.6 cP. Some symptoms of WM are attributable to tissue deposition of IgM, not to increased serum viscosity. IgM deposits may occur in kidney (glomeruli), intestine, and skin, leading to proteinuria, diarrhea, and characteristic papules (IgM storage papules or cutaneous macroglobulinosis)\[^14,15\], respectively. Kidney involvement usually leads to slowly progressive loss of function, rather than acute renal failure\[^16,17\]. Primary amyloidosis due to monoclonal light chain deposition has been found, in descending order of frequency, in the heart, peripheral nerves, kidneys, soft tissues, liver, and lungs\[^18\]. In contrast, secondary (reactive) amyloidosis is rarely seen\[^19\]. WM patients may also exhibit symptoms that are attributed to autoantibody activity of IgM. IgM \(\kappa\) with specificity to certain red blood cell antigens may lead to chronic immune hemolytic anemia that is associated with elevated cold agglutinin titers\[^20,21\]. The combination of mIgM, urticaria, fever, and arthralgia is known as Schnitzler syndrome\[^22\]. Neuropathies, which are caused in part by immunoreactivity of IgM to myelin–associated glycoprotein (MAG)\[^23\], IgM–mediated glomerulonephritis, angioedema, and acquired von Willebrand disease have all been reported. A laboratory finding without adverse health effects in approximately one fifth of patients with WM is the propensity of IgM to undergo precipitation at temperatures below normal body temperature; e.g., during storage of serum at 4°C in a refrigerator. However, in a small subset of cases (<5%), this phenomenon, known as cryoglobulinemia, causes symptoms including Raynaud syndrome, joint pain, and purpura and other skin changes\[^24\]. WM symptoms attributable to mIgM are presented in Fig. 2, right.
DIFFERENTIAL DIAGNOSIS

As depicted in Fig. 1, neither the presence of a malignant LPC clone in bone marrow nor the detection of an IgM spike in serum is pathognomonic for WM. Other IgM malignantities of the mature B-cell lineage, which are related to WM but also exhibit distinguishing features, may cause WM-like changes. Splenic marginal zone lymphoma (SMZL) appears to be a particular concern and is a frequent challenge for diagnosticians. Additionally, mantle cell lymphoma (MCL), rare cases of IgM-producing multiple myeloma (IgM-MM), and B-cell chronic lymphocytic leukemia (B-CLL) must also be considered when patients present with symptoms suggestive of WM (Fig. 3). SMZL can be distinguished from WM on the basis of immunophenotypic and molecular cytogenetic findings: CD11c (integrin alpha X chain) is more highly expressed in patients with SMZL, whereas CD25 (IL-2 receptor alpha chain) is twice as common in WM. CD103, a member of the integrin adhesion surface receptor family of protein, is invariably absent on WM cells but detected in 40% of patients with SMZL. The genomic abnormality most common in SMZL, loss of 7q31–32, is not seen in WM. Additionally, SMZL exhibits a specific gene expression signature upon genome-wide analysis of the tumor transcriptome using microarray technology. MCL can be distinguished from WM based on clinicohistopathologic findings and, in terms of cancer cytogenetics, the almost invariable occurrence of the hallmark t(11;14)(q13;q32) translocation that recombines IGH (Ig heavy-chain locus) on chromosome 14 and CCND1 (cyclin D1) on chromosome 11. MCL cells typically express SOX11 (SRY–box 11) and IgM myeloma can be distinguished from WM by virtue of its pronounced plasma cell morphology and presence of lytic bone lesions. Renal insufficiency is more common in IgM-MM than in WM. Chromosomal translocations involving IGH, particularly the cyclin D1–activating t(11;14)(q13;q32) exchange mentioned above, occur in IgM-MM but not WM. B–CLL may mimic WM clinically, but the morphological and immunophenotypic features of the tumor cells are usually sufficiently different from WM to avoid confusion. CLL is positive for CD5 (surface protein that mitigates activating signals from the B-cell receptor) and CD23 (low-affinity IgE receptor) by flow cytometry. Another area of concern from a diagnostic and clinical management point of view is the possibility that the low-grade lymphoma, WM, progresses to the high-grade lymphoma, diffuse large B-cell lymphoma (DLBCL). This is usually associated with aggressive clinical course, profound cytopenias, extramedullary disease, and poor outcome. The potentially diverse nature of "histological transformation events" in patients with WM, including those involving EBV (Epstein–Barr virus) infection, is increasingly recognized. In summary, care must be taken when the diagnosis of WM is established and signs of tumor progression to enhanced malignancy may not be missed.

RISK STRATIFICATION AND PROGNOSIS

Owing to novel agents and newly designed combination therapies briefly discussed in the following chapter, overall survival of WM patients of all ages has improved. Nonetheless, WM remains an incurable disease that exhibits significant variations in its clinical course and outcome. The latter is probably caused in large part by tumor–intrinsic differences with respect to genetic, epigenetic and biological determinants of tumor growth and tumor maintenance, on the one hand, and the pace and magnitude of IgM production, on the other. For disease staging, the International Prognostic Scoring System for WM has been developed. It uses five determinants: age (above 65 is a negative risk factor), hemoglobin (≤ 115 g/L), platelets (≤ 105 per
microliter), β 2 microglobulin (>3 mg/L) and mIgM (>70 g/L). After assessing one point for each negative risk factor, the patient can be categorized as low risk (≤ 1 except age), intermediate risk (2 or older than 65 yrs) or high risk (>2). The 3 risk groups are associated with a median survival of more than 10 years (143 months), ~8 years (99 months) and ~3.5 years (44 months), respectively. Age has a profound impact on risk stratification and prognosis because, as mentioned above, patients older than 65 years cannot be assigned to the low-risk category no matter how subdued the disease might be. In comparison to age, IgM levels are weighed more forgivingly, as this parameter does not enter the staging system until a threshold of 70 g/L is exceeded. Since mlgM levels correlate with abundance of monocytic plasma cells in bone marrow [46], the disease has significantly progressed at this juncture. Ongoing efforts to refine the staging system focus on serum levels of lactate dehydrogenase, which have been recently shown to stratify high-risk patients into two subgroups with significantly different outcomes [47, 48], and the immunoglobulin free light-chain assay, which is under review as a potential prognosticator of patients with WM [49]. Importantly, the value of the prognostic scoring/staging system for making treatment decisions for patients with WM remains unproven, even though it has been independently validated and is widely used for patient stratification in trials [50]. The design of the treatment plan remains therefore the prerogative of experienced clinicians who will first determine—based on the available clinical and laboratory findings, and taking the patient’s preferences into account—whether the patient requires therapy or is better off with watchful waiting. Taking the scoring/staging system into account, the newly updated Mayo Clinic mSMART guidelines categorize WM patients into 3 groups of increasing disease severity and outcome risk, based on hemoglobin levels, platelet numbers, presence of WM-related complications and other features (Fig. 4, left). With regard to overall outcome of WM, it is important to realize that WM takes an indolent course and patients with WM usually are of an advanced age. In fact, nearly half of them succumb to diseases of the elderly population—unrelated to WM [13]. This led to the introduction of cause-specific survival as an important outcome measure for WM, which censors (disregards) patients who die of causes other than WM [51]. Using this metric, the median disease-specific survival of WM patients in the United States is at least 10 years [51], with further improvement likely thanks to newly developed, practice-altering treatment regimens for WM briefly described in the following.

<table>
<thead>
<tr>
<th>Diagnosis:</th>
<th>Treatment:</th>
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<tbody>
<tr>
<td>IgM MGUS</td>
<td>None</td>
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<tr>
<td>Smoldering WM</td>
<td>Observation</td>
</tr>
<tr>
<td>Hemoglobin ≥ 11 g/dL</td>
<td>Rituximab(R)</td>
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<tr>
<td>Platelets ≥ 120,000/μL</td>
<td>1 cycle</td>
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<tr>
<td>Hemoglobin &lt; 11 g/dL</td>
<td>No maintenance</td>
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<tr>
<td>Platelets &lt; 120,000/μL</td>
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<tr>
<td>IgM-related neuropathy</td>
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<td>Hemolytic anemia</td>
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<tr>
<td>Cryoglobulinemia</td>
<td></td>
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<tr>
<td>Bulky disease</td>
<td>4–6 cycles BR</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL</td>
<td>(bendamustin+R)</td>
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<tr>
<td>Platelets &lt; 100,000/μL</td>
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</tr>
<tr>
<td>Hyperviscosity</td>
<td>No maintenance</td>
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<tr>
<td>Constitutional symptoms</td>
<td></td>
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<td>Group 1</td>
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<td>Group 2</td>
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<td>Group 3</td>
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**Fig.4**. Stratification of treatment-naïve WM patients as defined by the 2016 Mayo Clinic mSMART guidelines. Symptomatic WM arises in patients with the asymptomatic precursor conditions, IgM monoclonal gammopathy of undetermined significance (MGUS) and smoldering WM (SWM). The bone marrow in individuals with IgM MGUS and SMM contains less and more than 10% LPCs, respectively. Group 1 WM patients are managed with a “wait and watch” approach (observation) even if the size of the serum mIgM increases. Group 2 patients, who may exhibit WM-associated anemia and symptomatic cryoglobulinemia, will be treated with 1 cycle of single-agent rituximab (R) without subsequent maintenance therapy. If hyperviscosity develops under treatment with R, plasmapheresis will be performed. Group 3 patients with profound cytopenia and constitutional and/or hyperviscosity symptoms, receive 4–6 cycles of BR (bendamustin and rituximab) without maintenance therapy. As in the previous group, plasmapheresis is only indicated when hyperviscosity symptoms are present. Hematopoietic stem cells should be harvested in case the patient is a potential candidate for autologous bone marrow transplantation at a later time and is less than ~70 years of age and fit enough for the procedure.

**TREATMENT**

Treatment of WM should be reserved for symptomatic patients. Several therapeutic protocols are available: they have been competently designed by experts in the field and published in leading peer-reviewed hematology journals [13, 52–55]. The Mayo Clinic mSMART guidelines from 2016 recommend the monoclonal antibody to CD20 (rituximab) for frontline therapy of newly diagnosed Group 2 patients and a combination regimen of rituximab and bendamustine (BR) for Group 3 patients (Fig. 4, right). The nitrogen mustard–related alkylating agent bendamustine is a cheap, simple, and almost forgotten drug that had been developed as early as 1963 in what was the former German Democratic Republic (GDR), where it remained dormant and unavailable to the Western world until the reunification of Germany in 1990.
The drug has recently experienced a renaissance in the treatment of WM and related low–grade lymphomas [56,57]. For example, phase 3 data from the Study Group Indolent Lymphomas (StiL) trial showed that BR is a suitable frontline regimen with superior toxicity profile and longer progression free survival (PFS) relative to treatment using the R–CHOP (rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone) protocol [58]. Although a nearly complete (~95%) overall response rate (ORR) was evident for both regimens, better tolerability and longer PFS (69.5 months median) were seen in the BR arm [59].

For off–study salvage therapy of patients with relapsed or refractory WM (RRWM) [60], the mSMART guidelines recommend the repeat of the frontline (initial) therapy, monotherapy using ibrutinib, or one of two rituximab–containing triple–drug regimens: DRC (dexamethasone + rituximab + cyclophosphamide) or BDR (bortezomib + dexamethasone + rituximab). Treatment decisions depend on several factors, beginning with a clear need to reinitiate therapy in the first place. The number of prior regimens and the quality and durability of the remission that preceded the relapse must also be factored in. The patients’ eligibility for and willingness to undergo an autologous stem cell transplantation (ASCT) must also be considered. In 2015 ibrutinib received approval for the treatment of patients with WM in the United States and Europe based on results from a phase 1 trial with advanced B–cell malignancies [59] and a phase 2 trial with relapsed or refractory WM [60,61]. The cost of the drug at this juncture is high, yet its potential for increased future use as a stem cell–sparing pill in WM treatment is also high. A recent study on DRC for the treatment of RRWM concluded that this regimen is highly effective and well–tolerated. Additionally, compared to ibrutinib, DRC offers the advantage of lesser cost, fixed–duration therapy and, possibly, therapeutic efficacy that is not dependent on the presence of somatic mutations in MYD88 [62]. As mentioned above, ASCT—highly effective but underutilized in Western countries [63]—may be considered for eligible patients with WM.

The management of IgM–dependent hyperviscosity syndrome (HVS) involves plasmapheresis, which is able to acutely rid the patient serum of the abnormal immunoglobulin, is safe and effective, and is usually well tolerated [64]. Randomized, controlled clinical trials for treatment of serum HVS are lacking, but plasmapheresis is widely accepted as an effective short–term treatment for patients with WM [65]. A very recent, interesting development in the treatment of WM–dependent anemia is parental iron administration [66]. Investigational agents to further improve the outcome of WM in coming years [67,68] include monoclonal antibodies such as the fully humanized anti–CD20, ofatumumab, and antibody to CD52, alemtuzumab [69], immunomodulatory agents, such as thalidomide [70] and lenalidomide [71]; proteasome inhibitors including bortezomib, ixazomib and carfilzomib; the next–generation Bruton tyrosine kinase inhibitor, acalabrutinib; and molecularly targeted small–molecule inhibitors of cellular signal transduction pathways, such as the mTOR (mammalian target of rapamycin) inhibitors everolimus [72] and perifosine, the AKT (v–akt murine thymoma viral oncogene homolog 1) inhibitor perifosine [73] and the HDAC (histone deacetylase) inhibitor panobinostat [74].

**KEY POINTS AND IWMF–COORDINATED INTERNATIONAL PATIENT SUPPORT GROUPS**

WM is a low–grade blood cancer of the mature B–lymphocyte lineage that is closely related to, but distinct from, other low–grade B–cell lymphomas including SMZL, MCL and B–CLL. The features of WM and its differential diagnosis are well established. The treatment of WM is highly effective and long–term control with good clinical management is possible. Nevertheless, WM remains an incurable neoplasm at this juncture. Experienced WM clinicians increasingly emphasize the circumstance of long survival and advanced age of the great majority of patients with WM, which calls for greater attentiveness for quality–of–life and treatment–associated morbidity issues. Selecting the most appropriate interventions for patients with WM and managing the complications of the progressive disease remain ongoing tasks.

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**Fig. 5. Salvage therapies for relapsed or refractory WM (RRWM) according to mSMART guidelines.** Retreatment with the initial therapy can be considered if the time to next therapy (TTNT) exceeds 3 years after initial or previous therapy. Encouraging clinical outcome data from combination therapy using DRC or BDR and monotherapy using ibrutinib are available. ASCT is an option but its optimal timing is not established and—due to indolent disease course, advanced age, and multiple comorbidities—a large proportion of transplant candidates are ineligible. This renders unbiased trials that compare transplantation and conventional treatment approaches difficult. Novel agents for treatment of WM are in clinical development.

* Repeat original therapy if TTNT > 3 years
* DRC (dexamethasone + rituximab + cyclophosphamide)
* Ibrutinib monotherapy
* ASCT
* Novel agents
Expert reviews providing tons of valuable information on clinical aspects of WM are available. This includes a highly recommended and updated guideline on the diagnosis and management of WM that has been developed by experts at the Mayo Clinic in the United States and dubbed mSMART—an acronym for Mayo Stratification of Macroglobulinemia and Risk–Adapted Therapy. Importantly, patients with WM throughout the world are supported by a not-for-profit patient advocacy organization called the International Waldenström Macroglobulinemia Foundation (IWMF). The IWMF, headquartered in Florida, has affiliate organizations in Asia, Australia, Europe and the Americas, yet the People’s Republic of China is grossly underrepresented given that there is currently but one support group in Taiwan led by Dr. Jyh-Seng Wang. The IWMF supports all WM patients, their families, caregivers, and others with an interest in the disease. Additionally, it provides country-specific information and/or educational programs to address patient concerns and funds research towards finding a cure for WM.

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