



Review Article

Waldenstrom's Macroglobulinemia: An Update

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Abstract. Waldenstrom Macroglobulinemia is a rare lymphoproliferative disorder with distinctive clinical features.

Diagnostic and prognostic characterisation in WM significantly changed with the discovery of two molecular markers: MYD88 and CXCR4. Mutational status of these latter influences both clinical presentation and prognosis and demonstrated therapeutic implications.

Treatment choice in Waldenstrom disease is strictly guided by patients age and characteristics, specific goals of therapy, the necessity for rapid disease control, the risk of treatment-related neuropathy, disease features, the risk of immunosuppression or secondary malignancies and potential for future autologous stem cell transplantation.

The therapeutic landscape has expanded during the last years and the approval of ibrutinib, the first drug approved for Waldenstrom Macroglobulinemia, represents a significant step forward for a better management of the disease.

Keywords: Waldenstrom Disease, Macroglobulinemia, Ibrutinib, Treatment-related Neuropathy.

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Introduction. Waldenstrom Macroglobulinemia (WM) is a lymphoproliferative disorder characterized by the proliferation of lymphoplasmacytic elements in the bone marrow and the presence of monoclonal immunoglobulin M (IgM) gammopathy.¹

The World Health Organization (WHO) classification defined WM as lymphoplasmacytic lymphoma (LPL) secreting IgM proteins, belonging to the category of Non-Hodgkin B Lymphomas (NHL) with indolent course.²

The disease is rare, representing approximately 2% of all cases of non-Hodgkin Lymphoma,³ and presents distinctive clinical and laboratory features related to the presence of the monoclonal IgM.

Clinical presentation of WM is extremely heterogeneous, while some signs and symptoms are secondary to organ infiltration by clonal cells,

including anaemia, lymphadenopathy and splenomegaly, others are due instead, to specific immunological and physiochemical features of monoclonal IgM, such as neuropathy, hyperviscosity, and cryoglobulinemia.⁴

Despite the indolent disease course sometimes WM may require prompt treatment to avoid irreparable organ damage or fatal complications, such as in the case of hyperviscosity syndrome.⁵

Several therapeutic novelties have radically changed MW scenario during the last years.

Furthermore, the recent discoveries of two mutations, myeloid differentiation primary response 88 (MYD88) and C-X-C chemokine receptor type 4 (CXCR4) in WM patients has improved disease characterisation helping to deeper understand the biology of the disease.^{6,7}

In this review, we describe the main features of WM in the light of the new findings and current management of the disease including emerging therapeutic options.

Clinical Presentation. Apart from the systemic symptoms common to all NHL, MW clinical features can be secondary to organ involvement, as well paraprotein-related.⁴

The most frequent clinical sign of bone marrow infiltration is anaemia, that represents itself as the most common indication for treatment initiation. Nevertheless, several conditions, other than marrow replacement, may lead to low haemoglobin level and should be excluded before starting treatment.⁸

Anaemia may be related to absolute or functional iron deficiency, that can be distinguished by low iron saturation despite normal or high serum ferritin levels. Ciccarelli et al.⁹ attributed this event to hepcidin secretion by WM cells; the same findings were confirmed by Treon et al.¹⁰ who reported an excess of serum hepcidin in WM patients. Taking into account this evidence, intravenous iron infusion, instead of oral supplementation can be useful in some selected cases.

Haemolysis can occur in Waldenstrom. A haemolytic diagnostic workup is necessary in case of suspected haemolytic anaemia, including cold agglutinin titres, direct Coombs test, haptoglobin, lactate dehydrogenase and reticulocyte count.¹¹

Similarly to other NHL, organ infiltration by lymphoid clonal cells can lead to hepatosplenomegaly, lymphadenopathies and less frequently the involvement of extranodal tissues.¹²

Notably, IgM paraprotein itself can be responsible for several clinical pictures. High IgM serum level, over 4000 mg/dl, represents a risk factor for symptomatic hyperviscosity syndrome, a particular condition caused by increased serum viscosity.¹³⁻¹⁵ This complication occurs in 5-10% of patients at the time of diagnosis.¹⁶

In a recent retrospective study on 825 newly diagnosed WM patients, a serum IgM level >6000 mg/dl at diagnosis was associated with a median time to symptomatic hyperviscosity of 3 months, whereas the median time for patients with serum IgM level of 5000-6000 mg/dl was approximately three years.¹⁷ These findings may support the use of serum IgM level >6000 mg/dl as a criterion for

therapy initiation in an otherwise asymptomatic WM patient.

Hyperviscosity manifestations are heterogeneous and may include spontaneous epistaxis, ocular and hearing disorder, such as blurred vision, headache, tinnitus and vertigo. An increase of viscosity involving microcirculation, also in the central nervous system, can lead to clinical emergencies.¹⁵

In case of IgM levels >3000 mg/dl, even in the absence of clinical manifestations, the fundoscopic examination is recommended to reveal early signs of micro circular damage.¹⁷⁻¹⁸

IgM related immunological properties can also lead to particular situations.

Type I and II cryoglobulinemia can clinically emerge with skin alterations like purpura, ulcers and livedo, especially in the lower extremities. Moreover, the presence of cryoglobulinemia can also worsen hyperviscosity manifestations.¹⁹

IgM paraprotein related peripheral neuropathies (IgM - PN) are a heterogeneous group of disorders frequently associated with IgM monoclonal gammopathies including WM.²⁰

The Last International Workshop on WM (IWWM) consensus panel, identified six distinct entities of paraprotein-associated neuropathies.²¹

The presence of anti-MAG antibodies or IgM antibodies directed to other neural antigens (such as GD1a, GD1b, GM2) can lead to demyelinating and slowly progressive predominantly distal neuropathy.²² High titre of anti-GM1 antibodies otherwise, can be associated with a multifocal motor neuropathy.²³ High titre of antibodies against disialylated gangliosides (GQ1b, GT1a, GT1b, GD1b, GD2 and GD3) in the presence of neuropathy with ophthalmoplegia and ataxia may configure CANOMAD (Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl ganglioside antibodies) syndrome.²⁴ Finally, AL amyloidosis and small fibre neuropathies should always be considered as a possible cause of a paraproteinaemic neuropathy. In AL amyloidosis, symptoms are due to direct paraprotein infiltration, and clinical manifestations are progressive, painful small fibre predominant length-dependent and typically starting in the feet, accompanied by an autonomic neuropathy in about 65% of cases.²⁵ Small fibre symptoms, presenting as patchy dermatomal sensory disturbance subsequently coalescing are due to small fibre involvement of the sensory ganglia.²⁶

Other disorders can be generated from the deposition of IgM-secreting lymphoplasmacytic elements: amyloidosis is a rare and severe complication in MW. The organs most commonly involved are kidneys, heart, liver and peripheral nerves.²⁷

Two different and distinctive syndromes are rarely associated to MW.

The central nervous system involvement, called Bing-Neel syndrome, is a complication involving almost 1% of patients with WM. Heterogeneous neurological signs and symptoms may be investigated by the brain and whole spine imaging and cerebrospinal fluid tests.²⁸

Schnitzler syndrome is a chronic autoimmune urticaria associated with IgM gammopathy and other rheumatic manifestations, such as recurrent fever, joint and bone pain, characterized this autoinflammatory disorder.²⁹

Diagnosis. Diagnosis of WM requires the histologic evidence of bone marrow infiltration of lymphoplasmacytoid elements and the serum presence of monoclonal IgM gammopathy. The need of at least 10% LPL infiltration as a cut-off to distinguish WM from IgM monoclonal gammopathy of undetermined significance (MGUS), was emphasised by the Mayo Clinic consensus.³⁰ That is in contrast to the Second International Workshop Criteria that do not mandate a minimum requirement of the BM involvement to confirm the diagnosis.¹

Since the presence of serum IgM paraprotein itself is not specific and can be highlighted in a variety of small B-cell lymphoproliferative disorders, such as chronic lymphocytic leukemia and marginal zone lymphoma (MZL), as well as in rare cases of IgM myeloma (MM), the diagnosis of WM should be formulated combining specific histologic features, flow cytometry parameters and molecular markers.

Bone marrow biopsy shows lymphoplasmacytic and plasma cells; infiltration can be diffuse, interstitial or nodular, while purely paratrabecular pattern is uncommon.² Nevertheless, Bassarova et al. described as distinguishing features of LPL at variance to MZL, the focal paratrabecular involvement, the presence of lymphoplasmacytoid cells, Dutcher bodies ($P < .001$) and the increased numbers of mast cells.³¹

Immuno-phenotype reveals a clonal population of CD19, CD20, CD22, CD25, CD27, CD38,

CD79a, FCM7 and IgM surface/cytoplasmic IgM positive elements. Immunohistochemistry demonstrates lymphocytes and lymphoplasmacytic cells expressing IgM, with kappa or lambda restriction, CD19, CD20, weak CD22 and CD25. Few cases, 10-20%, can be CD5, CD23 or CD10 positive. Plasma cells in WM are CD38 and CD138 positive but do not show myelomatous antigen aberrations.³²⁻³⁴

There are no specific chromosomal aberrations associated specifically with WM. However, the frequency of individual chromosomal abnormalities differs from that in other lymphoproliferative disorders such as MZL or CLL.³⁵

In particular, 6q deletions and trisomy 4, that seems to be significantly associated with trisomy 18, are frequent in WM while translocations involving the IGH gene are very rare.³⁶ Furthermore, the t(11;14) translocation, recurrent in IgM MM, does not occur in WM.³⁷ The prognostic value of these abnormalities, especially 6q deletion, is still controversial.^{38,39}

In 2012 Treon et al. revealed the presence of a MYD88 L265P mutation in the majority of patients with WM and this brought new insights in the diagnosis and treatment of the disease. MYD88 is an adaptor molecule in Toll-like receptor (TLR) and interleukin 1 receptor (IL-1R) signalling. Following TLR or IL-1R stimulation, MYD88 is recruited to the activated receptor complex as a homodimer and its association with IRAK4 activates IRAK1 and IRAK2. Tumor necrosis factor receptor-associated factor 6 is then activated by IRAK1, leading to nuclear factor κ B (NF- κ B) activation via I κ Ba phosphorylation and neoplastic cell growth and survival. The MYD88 L265P somatic mutation has been identified in >90% of WM patients by whole-genome sequencing.⁴⁰ However, the mutation has also been demonstrated in about 10% of MZL and other lymphoproliferative disorders, so it can't be used as a sole marker in the distinction of WM. Nevertheless, it is absent in IgM multiple myeloma and can be used for the differential diagnosis of these two diseases.⁴¹ Interestingly, the discovery of MYD88 L265P in IgM MGUS patient may suggest that this mutation could be an early oncogenic driver playing a role in disease progression to WM.⁴² Recently, Yang and colleagues showed that Bruton tyrosine kinase (BTK) was also activated by MYD88 L265P.⁴³

The diagnostic role of this mutation has been validated in several studies.⁴⁰⁻⁵⁰ Recently Hunter et al. identified the first ever reported somatic mutation in human cancer involving CXCR4.⁵¹ This mutation is present in 30% of WM patients and involves the C-terminus that contains serine phosphorylation sites which regulate signalling of CXCR4 by its only known ligand, stromal derived factor-1a (SDF-1a) (CXCL12). Germline mutations in the C-terminus of CXCR4 in WHIM patients block receptor internalisation after SDF-1a stimulation in myeloid cells resulting in persistent CXCR4 activation and bone marrow myeloid cell trafficking.⁵² Two different types of CXCR4 mutations have been identified: nonsense (CXCR4WHIM/NS) mutations that truncate the distal 15 to 20 amino acid region, and frameshift (CXCR4WHIM/FS) mutations that compromise a region of up to 40 amino acids in the C-terminal domain.⁵¹

The presence of CXCR4WHIM/NS mutation enhances AKT, ERK, and BTK signalling and increases cell migration, adhesion, growth, and survival in WM cells.⁴⁶ Other recurrent somatic mutations described in WM include ARID1A, TRAF3, CD79B, TP53, and MYBBP1A as well as monoallelic deletions of PRDM2, BTG1, TNFAIP3, and HIVEP2. The acquisition of most of these mutation/deletions leads to NF- κ B signalling enhancement in response to MYD88 L265P.^{51,54,55}

Prognosis. Several publications have been reported with the aim to identify variables that could be associated with reduced survival in WM patients.⁵³⁻⁶⁰

Three population-based studies analysed survival data on large cohorts of patients. Significant shorter survival resulted to be related to older age. Nevertheless, a proportion of elderly patients died from causes unrelated to WM, while disease-specific survival exceeded six years even for patients > 75 years.⁶² Moreover, a significant improvement in survival over time has been reported in patients with WM during the last decade.^{63,64}

At present, the only validated prognostic scoring system for patients with WM is the International Scoring System for WM (ISSWM) that was proposed in 2009 for patients requiring treatment. Three groups of patients were identified by this score: low, intermediate and high risk,

showing, respectively, 87%, 68% and 36% five-year survival rates. The risk stratification could be identified by five covariates easily testable in clinical practice: age (> 65), level of beta 2-microglobulin (β 2M > 3 mg/L), anemia (hemoglobin \leq 11.5 g/dL), thrombocytopenia (platelet < 100.000/mm³) and serum monoclonal protein concentration (IgM > 7 g/dL).⁶⁵

Concerning molecular markers, the presence or not of MYD88 L265P mutation demonstrated an impact on survival as patients carrying MYD88 L265P showed a significant improvement on survival when compared to wild-type MYD88, thus independently from CXCR4 mutational status.⁵⁰

On the other hand, CXCR4 mutational status seems to modulate clinical presentation. In fact, patients with CXCR4 mutations present with a significantly lower rate of adenopathy, and those with CXCR4 nonsense mutations have an increased BM disease burden, serum IgM levels, and/or risk of symptomatic hyperviscosity, while patients with MYD88 mutation seem to have high BM disease involvement and serum IgM levels.^{50,66,67}

Several reports of familial clustering of patients affected by WM alone or with other malignancies showed a common predisposition for WM with other lymphoproliferative diseases. A familial MW was demonstrated in almost 20% of cases by Kristinsson et al.⁶⁸ Furthermore, in a large single-center study, 26% of 924 consecutive patients with WM had a first- or second-degree relative with either WM or another B-cell disorder.⁶⁹ The diagnosis of familial form represents an independent marker for disease progression being associated with a 1.3-fold increased risk of death compared to sporadic WM, with an increasing hazard ratio for each additional relative with a lymphoproliferative disorder (defined as WM, NHL, MM, CLL, or MGUS).⁷⁰ From a clinical point of view, greater BM involvement and baseline IgM level were observed in familial compared to sporadic WM, while no difference was noted in cytogenetic abnormalities or lymph node or spleen involvement.⁷¹

While a report described a younger age at diagnosis of WM in the familial cases,⁷¹ this observation was not confirmed in subsequent studies.⁷² In a single institution study, familial WM was associated with inferior response rates to rituximab-combination regimens and shorter time-

to-next therapy (TTNT) than the sporadic cases. Furthermore, time-to-progression (TTP) in familial WM was significantly shorter (21 vs 45 months for sporadic). However, superior outcomes with bortezomib-containing regimens were observed in patients with familial WM, regarding overall and major response rates and TTNT.⁷³

Treatment. Similarly to other indolent lymphomas, treatment is also indicated for WM only in case of symptomatic disease.

The Last Consensus on treatment initiation criteria has been recently published by the Eighth International Workshop on Waldenstrom Macroglobulinemia (IWWM).

Clinical and laboratory conditions defining symptomatic disease are listed in **table 1**.

Notably, some particular situations require urgent therapeutic approach, in particular

symptomatic hyperviscosity should be considered as a clinical emergency; plasmapheresis is indicated in such cases to reduce IgM protein and consequently the risk of permanent organ impairment. However, the benefit of this procedure is time-limited so plasmapheresis should be rapidly followed by an acting systemic treatment.⁷⁴

Disease-specific characteristics at the time of progression should guide treatment choice.

Given the rarity of WM, most of the current treatment regimens have been adopted from data derived from phase 2 studies and less often from prospective trials addressed to WM as well as to other indolent B-cell lymphomas including Waldenstrom.

Treatment response criteria and classification are reported in **table 2**.

Table 1. Indications for treatment initiation

Clinical Criteria	Laboratory Criteria
Systemic symptoms (recurrent fever, night sweats, weight loss, fatigue)	Symptomatic cryoglobulinemia
Hyperviscosity	Cold agglutinin anemia
Symptomatic or bulky (>/=5 cm in maximum diameter) lymphadenopathy	Immune hemolytic anemia and/or thrombocytopenia
Symptomatic hepatomegaly and/or splenomegaly	Nephropathy related to WM
Symptomatic organomegaly and/or organ or tissue infiltration	Amyloidosis related to WM
Peripheral neuropathy due to WM	Hemoglobin <=10 g/dL
	Platelet count <100 x 10 ⁹ /L

Table 2. Treatment response definitions

Response Category	
Complete Response (CR)	<ul style="list-style-type: none"> • Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease • Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response (VGPR)	<ul style="list-style-type: none"> • Monoclonal IgM protein is detectable >= 90% reduction in serum IgM level from baseline • Complete resolution of extramedullary disease • No new signs or symptoms of active disease
Partial Response (PR)	<ul style="list-style-type: none"> • Monoclonal IgM protein is detectable >= 50% but < 90% reduction in serum IgM level from baseline • Reduction in extramedullary disease • No new signs or symptoms of active disease
Minimal Response (MR)	<ul style="list-style-type: none"> • Monoclonal IgM protein is detectable >= 25% but < 50% reduction in serum IgM level from baseline • No new signs or symptoms of active disease
Stable Disease (SD)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • >= 25% increase in serum IgM level from lowest nadir (requires confirmation) * • and/or progression in clinical features attributable the disease

*An absolute increase of > 5 g/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion

Treatment Naïve. Treatment choice should take into account patients age and characteristics, specific goals of therapy, necessity for rapid disease control, risk of treatment-related neuropathy, immunosuppression, secondary malignancies, and potential for future autologous stem cell transplantation (ASCT).

In the elderly population with comorbidities, single-agent treatment may be considered a suitable approach.

CD20 that is exclusively expressed in B-cells is a suitable therapeutic target for B-cell malignancies, including WM.⁷⁵ Rituximab is a chimeric anti-CD20 MoAb and has been widely used as a single agent in WM. Two schedules have been evaluated for Rituximab single agent in WM, leading to an overall response rate (ORR) of 18 - 40% as standard regimen (375 mg/mq for a 4-week cycle) and 35 - 65% as extended course (375 mg/mq for additional 4 weeks administered 8 weeks apart). Furthermore, PFS resulted in 33% for a standard schedule with a median follow up of 15,7 months and maximum 89,5% for median follow up of 29 months for the extended course. It is noteworthy that the pitfall of these studies is the small number of patients.⁷⁶⁻⁷⁹

Notably, the median time to response with rituximab monotherapy is seven months, so such a slow time of action makes this drug unsuitable for patients with the urgency of treatment. Furthermore, the possible occurrence of “IgM flare”, defined as the transient increase of IgM serum level, typically occurring after 1 to 4 months following rituximab infusion, could even worsen some WM symptoms secondary to hyperviscosity. In the presence of IgM levels >4000 mg/dl plasmapheresis should be considered to prevent flare before rituximab administration.⁷⁴ On the other hand, single-agent rituximab represents a valid option in the presence of immunologic disorders related to MW, such as symptomatic cryoglobulinemia, haemolytic anaemia or isolated IgM related peripheral neuropathy.^{74,80} A recent publication demonstrated a significant clinical improvement in almost half of the patients with anti-MAG antibody neuropathy treated with Rituximab in monotherapy.⁸¹

Ofatumumab is a fully human IgG1-type anti-CD20 MoAb. Its ability to bind to both the small and large loop of the membrane antigen CD20 allows a prolonged dissociation rate. Compared to

rituximab, ofatumumab is able to produce a more significant CDC activity with a similar antibody-dependent cellular cytotoxicity activity. Ofatumumab has been approved for the treatment of Chronic Lymphocytic Leukemia,⁸² but its activity as a single agent has also been tested by Furman and colleagues in 37 WM patients, including nine naive treatment cases. Following the first infusion, ofatumumab was administered at 1000 or 2000 mg weekly for four infusions. Almost 60% of patients obtained a response with 35% achieving at least a PR.⁸³ Despite the fact that rituximab infusion-related toxicity can be a concern, leading to therapy interruption in a proportion of cases, Castillo et al. reported the successful administration of ofatumumab in 22 patients who discontinued a previous treatment with rituximab due to intolerance.⁸⁴

In the past, oral chlorambucil was a commonly used agent, resulting in at least a partial response in 75% of patients; despite this fact, a complete response was rare. A randomised trial comparing two different dosing schedules found no difference in terms of response and survival.⁸⁵

In 2013, three years followed up from a large randomized study comparing single agent chlorambucil to fludarabine in 414 patients with previously untreated progressive WM, was published.⁸⁶

Fludarabine compared to chlorambucil, resulted in a high although not statistically significant response rate. Nevertheless, fludarabine treatment led to a significantly improved PFS and duration of response (median 36.3 and 38.3 months, respectively, versus 27.1 and 19.9 months, respectively with chlorambucil). Median OS as well, was not reached in the fludarabine arm versus 69.8 months in the chlorambucil arm. Although a higher incidence of grade 3-4 neutropenia was observed among patients treated with fludarabine, second neoplasms, including hematologic malignancies, were significantly more frequent in the chlorambucil arm with a 6-year cumulative incidence rate of 20.6% versus 3.7% in the fludarabine arm.

Considering the slow response to chlorambucil treatment and the possible risk of secondary malignancies and myelodysplastic syndromes, this therapy should be reserved for elderly patients, not in need of rapid disease control.

As in other lymphoproliferative disorders rituximab is mostly used in combination treatment

and specifically associated in WM with several chemotherapeutic agents, including alkylators, purine analogues, bendamustine, and proteasome inhibitors.

The combination of rituximab, cyclophosphamide and dexamethasone (DRC), was explored in 2007 by Dimopoulos et al. This regimen demonstrated to be highly effective in WM patients showing 83% ORR, thus including 7% of patients achieving CR. Long-term follow up of this study was published in 2015; with a median follow up of 8 years, median PFS was 35 months and median time to next treatment (TTNT) resulted in 51 months.

The combination showed to be well tolerated with only 9% of patients experiencing grade 3 or 4 neutropenia, and with limited long-term toxicity. Considering the favourable toxic profile and patients outcome, DRC is regarded as a suitable combination treatment in the first line. However considering the long median time to response of 4.1 this regimen does not allow rapid disease control.⁸⁷⁻⁸⁸

Three studies evaluated the efficacy of fludarabine-based regimens as primary treatment in WM. Treon and colleagues⁸⁹ explored the combination of rituximab and fludarabine (FR) in 43 patients, including 27 treatment naive. Overall, 96.3% of patients showed a response which was 86% excluding minor response; these results were similar in treatment-naive compared to previously treated cases (16/43 patients). Notably, with a median follow up of 40.3 months, two years PFS was 67%. The addition of cyclophosphamide to FR⁹⁰ led to 79.1% ORR (MR 74%) in 43 patients; most of them (65%) received FCR as first-line treatment. Responses were durable; at a median follow up of 38.8 months PFS was not reached, and two years overall survival was 88.4%. Souchet et al.⁹¹ in 2016 published the results of a retrospective study with fludarabine, cyclophosphamide and rituximab (FCR) offered to 27 naive treatment patients. Overall response rate and three years PFS resulted in 88% and 96%, respectively. Cladribine combined with rituximab was administered in 29 patients (55% treatment naive) with symptomatic WM. The ORR rate observed was 89.6% in the whole population (93% in naive treatment cases) without any difference between newly or pretreated patients. Therapy was overall well tolerated as no major infections were reported and no patients developed transformation

to high-grade NHL nor myelodysplasia. With a median follow-up of 50 months, four patients relapsed; median time to treatment failure was not reached, but only the lower limit of its 95% confidence interval was estimated at 60.3 months.⁹²

Nevertheless, despite high efficacy regarding response rate, proportion of major responses and response duration, purine-analogues based combinations should be avoided as first-line treatment in younger patients due to the significant incidence of toxicity, risk of long-term secondary malignancies and the impact on stem cell harvest. On the other hand, in older patients, myelosuppression is the primary concern with these agents.

Bendamustine and rituximab association (BR) is at present one of the most common regimens used in the first-line treatment of WM patients. In phase III large trial, the German study group on indolent lymphomas compared BR vs rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).⁹³ Overall response rate was similar between the two regimens; nevertheless, BR demonstrated to be superior to RCHOP in terms of PFS (69.5 vs 28.1 months) and tolerability. Taking into account this evidence, BR was designated as the first-line choice in different international guidelines and expert recommendations,^{72,78} thus also considering the possibility to modulate the schedule of administration in elderly patients or case of renal impairment.⁹⁴

Combination strategies with proteasome inhibitors are also effective in WM. Bortezomib, dexamethasone and rituximab (BDR) combination has been tested in WM treatment-naive patients by Treon and colleagues obtaining 96% ORR, and PFS of 78.3% in median follow up of 22.8 months.⁹⁵ On long-term analysis, median PFS was reached at 66 months. Moreover, treatment was rapidly effective (median time to response 1.4 months) and so, deliverable to patients with urgent need of IgM drop. Nevertheless, the primary concern of bortezomib administered with the twice-week schedule was the high rate of discontinuation (60%) due to neuropathy.^{92,93}

A significant reduction of neurological toxicity was obtained with an alternative bortezomib administration explored by Ghobrial et. al. Weekly administration of bortezomib, in fact, led to 88% ORR and 79% one-year event-free survival (EFS)

with no grade 3-4 neuropathies reported.⁹⁷ The same bortezomib weekly schedule was employed in the BDR regimen, except the first cycle in which bortezomib was administered twice a week, allowing to obtain a low rate of neurological complication (7% grade \geq 3) and discontinuation

(8%) due to neurological side effects. Efficacy (ORR 85%) and duration of response (median PFS of 42 months) resulted slightly inferior to previous studies.⁹⁸

Table 3 summarises main regimens employed in previously untreated patients.

Table 3.

Author	Regimen	N. pts	Treatment response (%)	Survival rates	Med F/U (mo)
Dimopoulos 2002	Rituximab 375mg/m ² /weekly, 4 consecutive weeks	27 (15 untreated)	ORR 44% (40% untreated pts) MRR NR	PFS 33.3% (all pts)	15.7
Gertz 2004	Rituximab 375mg/m ² /weekly, 4 consecutive weeks	34	ORR 18% MRR 0%	mPFS 27 mo	NR
Dimopoulos 2002	Extended R: 375mg/m ² /weekly, 8 cycles at weeks 1-4 and 12-16	17	ORR 35% MRR 35%	PFS 41.2% OS 94.1%	16 - 40
Treon 2005	Extended R: 375mg/m ² /weekly, 8 cycles at weeks 1-4 and 12-16	29 (12 untreated)	ORR 65% MRR 48%	PFS 89.5%	29
Furman 2011	Ofatumumab: ofatumumab 300mg for week 1 and 1000mg for weeks 2-4 (G1) or 2000mg for weeks 2-5 (G2). If stable disease or minimal response at 16th week, additional 300mg for week 1 and 2000mg for weeks 2-5	37 (9 untreated)	ORR 66.7% PR 35%	NR	NR
Leblond 2013	chlorambucil 8 mg/m ² per day for 10 days every 28 days	170	ORR 36%	mPFS 27 mo	36 mo
	fludarabine 40 mg/m ² per day for 5 days every 28 days	169	ORR 46%	mPFS 38 mo	
Dimopoulos 2007	DRC: D 20mg IV followed by R 375mg/m ² IV on day 1. C 100mg/m ² PO bid on days 1-5. Repeated treatment every 21 days for 6 cycles	72	ORR 81.9% MRR 73.6%	2yr PFS 67% 2yr OS 81%	23.4
Treon 2009	R + Fludarabine: R 375 mg/m ² /week IV at weeks 1 to 4, 17, 18, and 30, 31 with 6 cycles of fludarabine 25 mg/m ² daily for 5 days at weeks 5, 9, 13, 19, 23, and 27	43	ORR 96.3% MMR 88.9%	2yr PFS 67%	40.3
Tedeschi 2012	R + Fludarabine + Cyclophosphamide: R 375 mg/m ² IV on day 1, fludarabine 25 mg/m ² , cyclophosphamide 250 mg/m ² IV on days 2-4, every 28 days, total 6 cycles	43	ORR 79.1% MRR 76.7%	PFS NR 2yr OS 88.4% 4yr OS 69.1%	38.8
Souchet 2016	FCR: R 375mg/m ² IV on day 1, F 40 mg/m ² PO on days 1-3, C 250 mg/m ² PO on days 1-3, every 4 weeks for total 6 course.	82	ORR 88% MRR 76%	3yr PFS 96% 3yr OS 96%	47
Laszlo 2011	Rituximab 375 mg/m ² on day 1 followed by s.c. cladribine 0.1 mg/kg for 5 consecutive days, administered monthly for 4 cycles	29 (16 untreated)	ORR 93.7%	NR	50
Rummel 2013	RB: B 90 mg/m ² on days 1-2 of a 4 week cycle + R 375 mg/m ² on day 1 of each cycle	22	ORR 93% CR 40%	mPFS 69.5 mo	45
Treon 2009	BDR: B 1.3mg/m ² IV, D 40mg on day 1, 4, 8, 11, and R 375mg/m ² on day 11, 4 consecutive cycles for induction, then 4 cycles, each 3 months apart, for maintenance therapy	23	ORR 96% MRR 83%	PFS 78.3% OS 100%	22.8
Ghobrial 2010	Bortezomib + R: Bortezomib 1.6mg/m ² on days 1, 8, 15 every 28 days total 6 cycles with R 375mg/m ² /weekly IV infusion on cycles 1 and 4	26	ORR 88% MRR 65%	1yr EFS 79%	14
Dimopoulos 2013	BDR: B 1.3mg/m ² IV on days 1, 4, 8 and 11 followed by weekly B 1.6mg/m ² IV on days 1, 8, 15, and 22 every 35 days for 4 cycles, followed by D 40mg and R IV 375mg/m ² in cycle 2 and 5	60	ORR 85% MRR 73%	mPFS 42 mo	42

B: Bendamustine; R: rituximab; D: dexamethasone; C: cyclophosphamide; F: Fludarabine ;ORR: overall response rate; MRR: major response rate; PR: partial remission; VGPR: very good partial remission; CR: complete remission; PFS: progression free survival; OS: overall survival; mPFS: median progression free survival; EFS: event free survival; NR: not reported

The last follow-up from this research has been published recently and showed, after a median follow-up of 86 months, a PFS of 43 months, while OS was still not reached.⁹⁹ The role of rituximab as maintenance needs to be established as, in the only published study on this topic, prolonged administration of rituximab seemed to extend PFS and OS despite a more pronounced incidence of upper respiratory tract infections and immunoglobulin reduction.¹⁰⁰

Salvage Treatment. Given the fact that WM is incurable, almost all patients will relapse after initial therapy.

Type of therapy used at the time of relapse is determined by the response to initial therapy and again patient and disease characteristics. There is a general consensus, as for other lymphoproliferative disorders, to repeat the original treatment according to response duration. In symptomatic patients relapsing > 3 years after initial therapy, the same procedure can be repeated.³⁰

On the other hand, for relapse occurring < 3 years after initial treatment, an alternative regimen should be administered.

Similarly to first-line treatment, in the setting of relapse and refractory WM patients too, single-agent rituximab showed to be effective. The response rate with rituximab administered for 4 or 8 cycles ranged between 31 and 60%; DOR was comparable to that reported in previously untreated setting and was prolonged by the extended schedule. Nevertheless, these experiences are limited to a restricted number of patients.^{74,77,98}

The efficacy and tolerability of bendamustine were evaluated in 2 retrospective studies addressed to WM. Treon et al. reported 83% ORR and a median PFS of 13 months in 30 patients treated with bendamustine with or without the addition of rituximab.¹⁰² Treatment was overall well tolerated, although prolonged myelosuppression occurred in patients who received previous PA therapy. Tedeschi et al. reported the outcome of 71 patients treated with BR with bendamustine given 50/70/90 mg.¹⁰³ The ORR was 90% with the great majority of cases obtaining an MR; responses were durable as, at a median follow up of 19 months, PFS was still not reached. It is noteworthy that, despite higher bendamustine dose correlated with better response quality, the achievement of CR/VGPR

did not statistically impact on survival. Median time to IgM halving was three months.

No significant toxicities were recorded with almost 70% of patients completing the planned six courses.

Although bendamustine-based regimens have been widely used in lymphoproliferative disorders, some concerns about safety are emerging. In general, severe skin reaction is a known risk associated with bendamustine, so that recommended preventive measures for tumour lysis syndrome have been updated to avoid allopurinol concomitant administration.¹⁰⁴ Moreover, nearly half of 234 patients evaluated in a retrospective analysis developed at least one infection, one third being severe.¹⁰⁵

Data coming from GALLIUM trial and presented at the ASH meeting in 2016, showed an unexpectedly higher rate of deaths in patients treated with bendamustine in association with both rituximab or obinutuzumab.¹⁰⁶

Moreover, very few data recorded in literature are long-term toxicities of this agent. Recently, Martin et al. reported long-term outcomes of 149 subjects treated with bendamustine in 3 clinical trials. With a median follow-up of 8.9 years, 23/149 patients developed 25 cancers, including 8 patients with myelodysplastic syndrome/acute myeloid leukaemia.¹⁰⁷

Rituximab combinations with purine analogues are effective, leading to high rate of responses with a median PFS exceeding 50 months.^{86-89,101} Nevertheless, as previously mentioned, myelosuppression as well as high rate of long term toxicities are major concerns with these agents confining the use to selected cases with high tumor burden and limited therapeutic options. Moreover, a retrospective study focused on the long term outcomes of patients treated with FCR or BR were reported in 2015.¹⁰⁹ Interestingly, although FCR showed a higher number of toxicities during treatment course, discontinuation rate was similar between the 2 regimens. Response rate and quality were also comparable nevertheless, PFS was significantly superior with FCR treatment although it did not diverge when considering only responding patients. Event free survival did not differ between FCR and BR when considering either the whole population or only responding patients. Notably, a significant higher proportion of patients in the FCR group developed a solid tumor or MDS/AML.

Results coming from DRC combination in the setting of previously treated patients were reported by Paludo et al in 2017.¹¹⁰ Overall response rate was 87% with 68% MR. Median PFS and time-to-next-therapy were 32 and 50 (95% CI: 35–60) months, respectively being comparable to survival results obtained in the setting of treatment naive patients. Notably, response achievement and

outcomes were independent of MYD88 mutation status.

Bortezomib remains a valid option in previously treated patients allowing to obtain response rate of 81% with a median time to IgM lowering of approximately 1 month.

Table 4 summarizes main regimens employed in previously treated patients.

Table 4.

Author	Regimen	N. pts	Treatment response (%)	Survival rates	Med F/U (mo)
Gertz 2004	Rituximab 375mg/m ² /weekly, 4 consecutive weeks	35	ORR 31.4% MRR 0%	PFS NR OS 71.4%	NR
Treon 2001	Rituximab 375mg/m ² /weekly	30	ORR 60% MRR 27%	mPFS 8 mo	NR
Treon 2011	Bendamustine + Rituximab or ofatumumab: B 90 mg/m ² IV on days 1, 2 total 6 cycles with R 375 mg/m ² IV on day 1 or 2 every 4 weeks or ofatumumab 1g IV on day 1	30	ORR 83.3% MRR 83.3%	NR	7.5
Tedeschi 2015	Rituximab 375 mg/m ² day 1 and Bendamustine (50-90 mg/m ²) days 1 and 2 every 28 days	71	ORR 80% MRR 75%	NR	19
Tedeschi 2013	R + Fludarabine + Cyclophosphamide: R 375 mg/m ² IV on day 1, fludarabine 25 mg/m ² , cyclophosphamide 250 mg/m ² IV on days 2-4, every 28 days, total 6 cycles	40	ORR 80% VGPR 33%	mEFS 77 mo	51
Paludo 2017	DRC: D 20mg IV followed by R 375mg/m ² IV on day 1. C 100mg/m ² bid on days 1-5. Repeated treatment every 21 days	50	ORR 87% MRR NR	mPFS 32 mo	NR
Ghobrial 2010	Bortezomib + R: Bortezomib 1.6mg/m ² on days 1, 8, 15, every 28 days for 6 cycles, R 375mg/m ² /weekly IV on cycle 1 and 4	37	ORR 62.2% MRR 86.5%	1yr PFS 58% 1yr OS 94%	16
Treon 2015	Ibrutinib: 420mg daily	63	ORR 90.5% MRR 73.0%	2yr PFS 69.1% 2yr OS 95.2%	NR
Dimopolous 2017	Ibrutinib: 420mg daily	31	ORR 90% MRR 71%	18mo PFS 86% 18mo OS 97%	18.1 mo
Treon 2008	daily thalidomide (200 mg for 2 weeks, then 400 mg for 50 weeks) and rituximab (375 mg/m ²) per week) dosed on weeks 2 to 5 and 13 to 16.	25	ORR 72% MRR 64%	mPFS 38 mo	NR
Treon 2009	R + Lenalidomide: 48 weeks of lenalidomide 25 mg/day PO for 3 weeks and then 1 week off along with R 375 mg/m ² /wk IV dosed on weeks 2 to 5 and 13 to 16	16	ORR 50% MRR 25%	PFS 25%	31.3
Treon 2014	KRD: carfilzomib 20mg/m ² IV for 1st cycle, then 36mg/m ² for 2nd cycle and beyond) + R 375mg/m ² on days 2 and 9 every 3 weeks for 6 cycles + D 20mg IV on days 1, 2, 8, and 9	31	ORR 87.1% MRR 67.7%	PFS 64.5% OS 100%	15.4
Ghobrial 2014	Everolimus: 10mg daily	50	ORR 70% MRR 42%	12mo PFS 62%	11.5
Ghobrial 2015	Everolimus+Bortezomib+R (phase I): everolimus 5 or 10 mg with R at 375 mg/m ² or with R and bortezomib at 1.3 or 1.6 mg/m ² for the phase I. Everolimus+Bortezomib+R (phase II): Everolimus 10mg daily, bortezomib 1.6mg/m ² IV weekly on days 1, 8, 15 ever 28 days, and R IV 375mg/m ² weekly on days 1, 8 15, 22 every 28 days in cycle 1 and 4 only.	46	ORR 87% MRR 50%	2yr PFS 42%	15
Ghobrial 2010	Perifosine 150 mg daily	37	ORR 35% MRR NR	mPFS 13 mo	NR
Ghobrial 2012	Enzastaurin 250 mg twice daily after a single loading dose (day 1, cycle 1) of 375 mg 3 times daily for 8 cycles of 28 days each	42	ORR 38%	NR	NR
Kahl 2010	Idelalisib at 150 mg twice daily	4	ORR 62%	NR	NR

B: Bendamustine; R: rituximab; D: dexamethasone; C: cyclophosphamide; K: carfilzomib; ORR: overall response rate; MRR: major response rate; VGPR: very good partial remission; PFS: progression free survival; OS: overall survival; mPFS: median progression free survival; EFS: event free survival; NR: not reported.

Despite considerable activity, it is noteworthy that response duration is short as in previously treated patients, median time to progression and time to next treatment were 16 and 17 months, respectively.¹¹¹

Ibrutinib. Up to now ibrutinib is the only agent that has been specifically approved by FDA and EMA for the treatment of WM.^{105,106}

In preclinical studies ibrutinib demonstrated its efficacy in the inhibition of I κ B-alpha phosphorylation resulting in NF- κ B signaling block. Notably, as BTK is a downstream target of MYD88 L265P signaling, ibrutinib exerts its action at higher levels in MYD88 L265P-expressing cells rather in wild-type cells.¹¹⁴

In a single-arm phase II trial, ibrutinib was administered to 63 previously treated patients with WM.¹¹⁵ Overall response rate was 91% with 73% MR in a median time to response of 4 weeks. Neutropenia, thrombocytopenia, anemia, atrial fibrillation and infection were the most commonly reported grade 3-4 adverse events. Based on these results, in January 2015 ibrutinib obtained FDA approval as a breakthrough therapy for WM.¹¹² Notably, response rate and quality significantly associated with genomic profile as all MYD88 L265P mutated/CXCR4 WT cases obtained a response with ibrutinib compared to 86% ORR among patients with MYD88 and CXCR4 mutations; furthermore, MR of patients carrying MYD88 but no CXCR4 mutations was 92% versus 62% in those who showed both mutations. Overall, only 71% of patients with WT MYD88 status achieved a response, that was minor in all the cases. At 37 months follow up, 10 among the initial 63 patients progressed and neither PFS nor OS was reached. The prognostic impact of MYD88 and CXCR4 mutational status was confirmed at longer observation. Moreover, compared to the initial report, no significant difference in terms of side effects was reported.¹¹⁶

Finally, INNOVATE is a single arm, multicenter, open-label, phase III study exploring ibrutinib efficacy and tolerability in 31 rituximab-refractory WM.¹¹⁷ Median number of prior therapies was four and 42% of patients were classified as high risk per the IPSSWM. Response rate and quality in such a high risk population was superimposable to that previously reported by Treon et al. (90% ORR with 71% MR). Once again, responses were rapid and durable. With a

median follow up of 18 months, estimated PFS and OS were 86% and 97%, respectively. Common grade 3-4 adverse events included neutropenia, hypertension, anemia, thrombocytopenia and diarrhea. Twenty six among the 31 patients were continuing with ibrutinib at the time of the report.

Despite much evidence of ibrutinib activity in Waldenstrom Macroglobulinemia, clinical progression occurs while on therapy. It has been demonstrated that WHIM-like CXCR4 S338X somatic mutation promotes resistance to ibrutinib through the activation of AKT and ERK signaling.¹¹⁸ Moreover, similarly to chronic lymphocytic leukemia, also in WM activating mutations in BTK^{cys 481}, PLC γ 2 and CARD11 were detected and were frequently identified in CXCR4^{WHIM-like} cases. Interestingly, some patients carrying subclonal BTK mutations, subsequently progressed while on treatment course. None of the mutations was found at baseline confirming that acquisition of mutations is probably linked to ibrutinib selective pressure on the leukemic clone.¹¹⁹

Novel Agents. Thalidomide and lenalidomide are immunomodulatory agents currently approved for the treatment of multiple myeloma.

Rituximab combined with thalidomide or lenalidomide produced 72% and 50% response rate, respectively.^{113,114} Nevertheless, late responses (median after 9 to 12 cycles) and development of acute anemia in more than 80% of patients, make this drug unsuitable for WM. On the other hand, thalidomide demonstrated an activity in WM only when administered at significantly higher dosages than in multiple myeloma and this fact, together with the well-known subclinical neuropathy that exists in patients with WM predisposes them to enhanced thalidomide-related neurotoxicity.

Pomalidomide could be a promising alternative to the other immunomodulatory agents and is currently under investigation in phase I clinical trials.

Carfilzomib, a second-generation selective proteasome inhibitor, showed a favourable toxicity profile in the myeloma setting and has also been explored in WM. Carfilzomib, rituximab and dexamethasone (CaRD) was administered as front line therapy in 28 patients and led to 87% OR

(36% VGPR or CR) and 64.5% PFS at 15.4 months. Responses were not affected by MYD88L265P or CXCR4WHIM mutation status. No severe neurological toxicity was reported.¹²²

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR)-signaling pathway showed to play a pivotal role on the initiation and progression of B cell malignancies, enhancing cell survival by stimulating cell proliferation, and inhibiting apoptosis.¹²³ Following *in-vitro* data, the efficacy of mTOR inhibitor everolimus has been explored in phase I-II trials.^{117,118} When used as single agent, everolimus led to about 70% ORR. Combinations of everolimus with bortezomib and/or rituximab allowed to achieve 74% ORR with 5% CR.¹²⁶ However, a considerable number of patients experienced grade >3 hematologic and non-hematologic adverse events including pulmonary toxicity. Taking into account such a safety profile, the use of this drug should be considered only in selected patients in the context of clinical trials.⁷⁴

Perifosine is an Akt Inhibitor leading to 35% ORR in 37 previously treated WM.¹²⁷ Median PFS was 12.4 months. Grade 1-2 gastrointestinal symptoms were reported in most of the patients; hematologic toxicity was also reported.

Enzastaurin is a serine/threonine kinase inhibitor that showed antiangiogenic, antiproliferative, and proapoptotic properties *in vitro* and antitumor activity *in vivo* in a xenograft WM model. Its efficacy was evaluated in a phase II study on 42 patients who received previous treatment for Waldenstrom disease. Almost 40% of patients obtained a response being major in 2 cases. Grade 3 leukopenia occurred in one case while 1 patient died due to a septic shock.¹²⁸

PI3K δ inhibitor idelalisib was evaluated in 4 WM in the context of a phase I trial addressed to relapsed/refractory NHL.¹²⁹ Overall, 62% of patients obtained a response. Nevertheless, a phase II trial with this agent was prematurely interrupted due to the recurrence of liver toxicity even when idelalisib was administered at lower dose level.¹³⁰

Venetoclax, a B-cell CLL/lymphoma 2 (BCL2) antagonist, was tested *in-vitro* on WM cells and was found to be effective in cell lines with CXCR4^{WHIM}. This BCL2 inhibitor, combined with ibrutinib and idelalisib, enhanced apoptosis in cell lines derived from WM patients presenting CXCR4^{WHIM} mutation.¹³¹ M12-175 trial, a phase I

study, tested venetoclax for the first time in patients with relapsed and refractory CLL and NHL. The BCL2 inhibitor demonstrated to be effective and well tolerated in all lymphoma subtypes including 4 patients with WM.¹³²

The increasing knowledge of disease biology allowed to recognise new potential therapeutic targets, such as CD38 that is expressed on the surface of almost half of WM malignant cells.¹³³ Daratumumab, a monoclonal antibody against CD38, approved for the treatment of multiple myeloma, is a promising agent for the treatment of WM.

Considering the increased expression of CXCR4 on WM cells, agents active against this molecule are actually on study.¹³⁴ Ulocuplumab, a fully human monoclonal antibody that targets CXCR4, was recently tested *in vitro* and *in vivo* studies on xenograft models: as monotherapy it showed antitumor activity against leukaemia, lymphoma and myeloma.¹³⁵ Therefore, strategies targeting CXCR4 may constitute an effective therapeutic approach for WM potentially providing benefit even in ibrutinib resistant cases.

Second generation BTK inhibitors include acalabrutinib, BGB-3111, CC292 and ONO-4059. These agents showed greater selectivity compared to ibrutinib and phase I/II trials addressed to patients with WM are ongoing. A phase III trial comparing BGB-3111 to ibrutinib in WM relapsed and refractory patients is also currently enrolling patients.

The role of maintenance in WM is under investigation: MAINTAIN trial is testing the efficacy on maintenance with rituximab after an induction therapy with bendamustine and rituximab.

Conclusions. The therapeutic landscape is expanding for Waldenstrom Macroglobulinemia. Treatment choice in first, as well in subsequent lines of therapy, should be driven by clinical features (age, comorbidities, concomitant medications, eligibility for transplant procedures), disease-specific characteristics at the time of progression and genetic profile.

The therapeutic objective should also be clear before starting treatment, as some agents leading to deeper responses and, in this way, to a prolonged survival, are often linked to a worse safety profile.

One of the main problems in treatment management of WM is that most of currently administered regimens, are extrapolated from studies involving indolent lymphoma while there is a lack of randomized prospective trials specifically addressed to WM.

Nevertheless, what clearly emerged from clinical trials is that first line treatment should always include rituximab. Patients receiving rituximab-based regimens compared to those who didn't in fact, showed significantly better OS without differences in hospitalizations or plasmapheresis. Moreover, survival appears not to differ when rituximab is administered alone or in combination with chemotherapy with similar outcomes when single agent rituximab is compared with either purine analogues or alkylating agents administered as monotherapies.¹³⁶

It is important to take into account disease-specific characteristics, at the time of treatment decision.

Rituximab alone or in combination, is a valid option for neuropathy although the occurrence of IgM flare could even worsen the neurologic clinical picture. In case of bulky adenopathies, the addition of bendamustine to rituximab is an effective regimen. Chemoimmunotherapy with DRC should be considered instead in elderly

patients, in the presence of cytopenia taking into account the reduced myelotoxicity of this regimen. Bortezomib and carfilzomib-based combinations are also effective in this setting and guarantee a rapid reduction of IgM levels together with improvement of cytopenia.

Ibrutinib is currently the only therapeutic agent approved for relapsed/refractory WM. Nevertheless, data on ibrutinib are very limited and ibrutinib resistance is getting more frequent while follow up is extending. Moreover, patients with unmutated MYD88 status are more likely to do worse with ibrutinib than with chemoimmunotherapeutic or proteasome inhibitor based combinations.

Considering the emergence of mutations, ibrutinib combinations with other biologic agents, acting on alternative ways of BCR signaling pathway, could be a reasonable option in order to avoid the occurrence of resistance. Besides MYD88, targeting of CXCR4-CXCL12 axis through CXCR4-antagonists may offer a complementary mode of action by affecting CXCR4-expressing tumor cells.

Finally, despite the rarity of the disease, large prospective international trials are warranted to better understand the most appropriate clinical use and long term side effects of new agents in Waldenstrom patients.

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