Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus


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Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder for which clearly defined criteria for the diagnosis, initiation of therapy, and treatment strategy have been proposed as part of the consensus panels of International Workshops on WM (IWWM). As part of the IWWM-7 and based on recently published and ongoing clinical trials, the panels updated treatment recommendations. Therapeutic strategy in WM should be based on individual patient and disease characteristics (age, comorbidities, need for rapid disease control, candidacy for autologous transplantation, cytopenias, IgM-related complications, hyperviscosity, and neuropathy). Mature data show that rituximab combinations with cyclophosphamide/dexamethasone, bendamustine, or bortezomib/dexamethasone provided durable responses and are indicated for most patients. New monoclonal antibodies (ofatumumab), second-generation proteasome inhibitors (carfilzomib), mammalian target of rapamycin inhibitors, and Bruton’s tyrosine kinase inhibitors are promising and may expand future treatment options. A different regimen is typically recommended for relapsed or refractory disease. In selected patients with relapsed disease after long-lasting remission, reuse of a prior effective regimen may be appropriate. Autologous stem cell transplantation may be considered in young patients with chemosensitive disease and in newly diagnosed patients with very-high-risk features. Active enrollment of patients with WM in clinical trials is encouraged. (Blood. 2014;124(9):1404-1411)

Introduction

Waldenström macroglobulinemia (WM) is, according to the World Health Organization classification, a lymphoplasmacytic lymphoma in which the bone marrow is infiltrated by immunoglobulin (Ig)M-producing clonal lymphoplasmytic cells. The Second International Workshop on WM (IWWM-2) proposed criteria for the clinicopathological diagnosis and for initiation of therapy in WM patients. The IWWM consensus panels have provided treatment recommendations, which were last updated in 2008 (IWWM-4). As part of its last consensus deliberations (IWWM-7, Newport, RI, August 2012), the panel considered the results from phase 2 studies of several chemoinmunotherapy regimens, novel drugs (alone or with rituximab), and emerging novel targeted agents (ofatumumab, everolimus, panobinostat, carfilzomib, and ibritumomab); examined these data; and updated its recommendations, which are presented herein.

The consensus panels recommended that individual patient considerations should be weighed for the choice of therapy, including the need for rapid disease control, age, candidacy for autologous transplantation, comorbidities, presence of cytopenias, hyperviscosity, lymphadenopathy, IgM-related end-organ damage, and patients’ preferences. Based on available data, the panel provides guidance on the management of patients with WM adjusted to specific conditions and complications of the disease both for the initial therapy and for relapsed or refractory disease.

Major changes since the last published recommendations

Rituximab-based regimens remain a recommended primary therapy for most patients with WM. As per the previous recommendations of IWWM-4, dexamethasone, rituximab, and cyclophosphamide (DRC) remains a primary choice, but combinations such as rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) are no longer considered a first-line choice; instead,
...bendamustine-rituximab (BR) is now a primary treatment option, especially for patients with high tumor bulk. In the current recommendations bortezomib-rituximab combinations may also be considered a primary option for patients with high-risk features (ie, hyperviscosity) or in younger patients for whom avoidance of alkylator therapy is sought. Fludarabine-based combinations are not recommended for primary therapy but remain an option for patients with relapsed/refractory disease with adequate performance status. In patients who may be candidates for single agent oral therapy, oral fludarabine (if available) is recommended over chlorambucil.

### Risk stratification

The importance of a prognostic system for the risk stratification of patients with WM and as a tool for study comparisons has been emphasized.\(^8\) In International Prognostic Scoring System for WM I (IPSSWM), 5 covariates (age $\geq$ 65 years, hemoglobin $\leq$ 11.5 g/dL, platelet counts $\leq$ 100 $\times$ 10\(^3\)/L, $\beta_2$-microglobulin $> 3$ mg/L, serum monoclonal protein $> 70$ g/L) defined 3 risk groups (low, intermediate, and high risk, respectively).\(^7\) IPSSWM has been validated externally, and its prognostic significance has been confirmed.\(^6,10\) Results per IPSSWM risk category are increasingly reported and are used for stratification in randomized clinical trials. However, the use of IPSSWM in making treatment decisions remains to be delineated.

### Justifying treatment initiation

Not all patients with a diagnosis of WM need immediate therapy. Criteria for the initiation of therapy (proposed in the IWWM-2 consensus panel and confirmed in IWWM-7) are presented in Table 1. For patients who do not fulfill the criteria in Table 1 and in whom only laboratory evidence may indicate a possible development of symptomatic disease (such as a minor decrease in hemoglobin level, but $> 10$ g/dL, or mild increases in IgM or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient), close observation is recommended.\(^3\)

### Risk assessment for progression to symptomatic disease and follow-up recommendations

IgM-monoclonal gammopathy of undetermined significance or asymptomatic WM are increasingly diagnosed because more individuals undergo a serum protein electrophoresis as part of a routine laboratory assessment. The diagnosis of asymptomatic WM requires the demonstration of infiltration of the bone marrow by $\geq$10% clonal lymphoplasmacytic cells on trephine biopsy or a monoclonal IgM $> 3$ g/dL and no end-organ damage or symptoms.\(^11\)

The median time to initiation of therapy for asymptomatic patients in the Southwest Oncology Group-S9003 study exceeded 7 years.\(^12\) In the series by Kyle et al, the cumulative probability of progression for patients with asymptomatic WM was 6%, 39%, 59%, and 68% at 1, 3, 5, and 10 years, respectively,\(^11\) and 75% required therapy during a median of 15 years of follow-up. Lower hemoglobin,\(^11,12\) extensive bone marrow infiltration,\(^11\) size of serum M-spike,\(^11\) and $\beta$-microglobulin levels\(^12\) were significant predictors of an eventual need for therapy.

There are no data to justify early initiation of treatment, and patients with asymptomatic WM should be followed without therapy, preferably every 3 months for the first year to evaluate the pace of disease progression and, if stable, at more extended intervals thereafter. The risk of progression remains, and individuals with asymptomatic WM should be followed for life.

### Evaluation of response to therapy

The consensus-based uniform response criteria for WM, based mainly on the degree of M-protein reduction, were recently updated\(^6,9,13\) (Table 2). Caution is advised in the early evaluation of response during rituximab-based therapy (or other anti-CD20 monoclonal antibodies), because of the common IgM flare,\(^14-16\) which does not necessarily imply disease progression; in most cases, it will resolve, but if necessary, additional tests may be performed to discriminate from disease progression. In patients treated with agents such as bortezomib or everolimus, tumor reduction in the bone marrow may not be proportional to the suppression of IgM levels.\(^17-20\) Thus, the variability of the IgM kinetics with various therapies should be taken into account, and in discordant cases, additional investigations should be considered.

### New treatment options for patients with WM

#### Bendamustine

In the study group of indolent lymphomas/non-Hodgkin lymphoma (StiL NHL) 1-2003 study, 513 newly diagnosed patients with follicular, marginal zone, small lymphocytic, and mantle cell lymphoma and WM received BR or R-CHOP: of 41 patients with WM, 22 received BR and 19 received R-CHOP.\(^21\) Responses were similar (95% in both arms), but BR was superior in terms of progression-free survival (PFS; median, 69.5 vs 28.1 months; $P = .0033$) and tolerability. After a median follow-up of 45 months, a difference in overall survival was observed after the fifth year, but further follow-up is needed. Regarding stem cell harvest, after 6 cycles of BR, the CD34 yield was similar to that after R-CHOP.

As part of a large study investigating rituximab maintenance in patients with previously untreated low-grade lymphomas (including WM), BR induction was given in 162 patients with WM (116 were evaluable for response), and 86% achieved at least partial response (PR).\(^22\) Responding patients (at least PR) were randomized to either observation or 2 years of rituximab maintenance; updated results are awaited.

Bendamustine is also active in patients with relapsed or refractory WM, either with rituximab, ofatumumab, or as monotherapy (very good partial response [VGPR] in 17%, PR in 67%; median PFS, 13.2 months), but prior nucleoside analog exposure was associated with prolonged myelosuppression.\(^23\)
Thus, available data indicate that BR is at least as effective as R-CHOP, may be associated with longer PFS and less toxicity, and probably does not compromise stem cell collection. However, R-CHOP is not a standard first-line regimen for WM, with less intensive and less toxic regimens like DRC are more often used. No increased incidence of secondary malignancies after BR was observed but longer follow-up is needed. BR is a primary option for patients with newly diagnosed WM, especially those in need for rapid disease control or with bulky disease.

### Bortezomib

Single agent bortezomib is associated with responses in ~40% of patients with relapsed or refractory WM, including fludarabine and rituximab refractory patients. Bortezomib with rituximab (±dexamethasone) are active, and in the front-line setting, 3 phase 2 studies of bortezomib/rituximab combinations showed response rates (at least PR) between 66% and 83% and rapid times to first response (2-3 months). Treon et al treated 23 previously untreated patients with 4 consecutive cycles of bortezomib, dexamethasone, and rituximab (BDR) using twice-weekly, intravenous bortezomib, followed by 4 additional cycles given at 3-month intervals (at least a median of 2 months, and the median PFS was 21 months). Among 59 previously untreated patients, 68% achieved at least PR (3% CR, 7% VGPR); IgM flare developed in 40% and 54% of patients who developed peripheral neuropathy, but in none was the grade ≥3. Dimopoulos et al, to avoid IgM flare, used an induction cycle of bortezomib (intravenous 1.3 mg/m² on days 1, 4, 8, and 11), followed by 4 cycles of weekly bortezomib (intravenous 1.6 mg/m² for 4 weeks) with rituximab and dexamethasone on cycles 2 and 5. Among 59 previously untreated patients, 68% achieved at least PR (3% CR, 7% VGPR); IgM flare occurred in 11%, but plasmapheresis was not required, probably due to the initial bortezomib induction. After a median follow-up of 42 months, responses were durable (median PFS was 42 months and 3-year PFS for those with at least PR was 70%), despite the lack of maintenance. Peripheral neuropathy was observed in 46% (grade ≥3 in 7%), but only 5 (8%) patients discontinued bortezomib due to neuropathy.

Neurotoxicity is the major concern with bortezomib because underlying IgM-related neuropathy or neuropathies due to age-related comorbidities (such as diabetes) are common. Weekly dosing and subcutaneous administration may reduce rates and severity of neuropathy and is explored in a clinical trial (NCT01592981). Bortezomib is not stem cell toxic, and long-term follow-up in myeloma patients does not suggest a risk for secondary malignancies. Prophylaxis against herpes zoster is strongly recommended. Primary therapy with bortezomib is recommended for patients with high levels of IgM, with symptoms of, or at risk of developing, hyperviscosity syndrome, symptomatic cryoglobulinemia or cold agglutininemia, amyloidosis, and renal impairment.

Carfilzomib, a second-generation proteasome inhibitor, is associated with a low risk of neurotoxicity in myeloma patients and was recently evaluated in combination with rituximab and dexamethasone (CaRD), mainly in untreated WM patients. The schedule of carfilzomib was attenuated (days 1, 2, 8, and 9) compared with myeloma dosing, and maintenance therapy (days 1 and 2 only) was given every 8 weeks for 8 cycles. The overall response rate was 87% (at least VGPR in 35%), and no grade ≥3 neuropathy was observed. With a median follow-up of 15.4 months, 20 of 31 (65%) patients remained progression free. CaRD therefore represents a novel neuropathy-sparing option for proteasome inhibitor-based therapy for WM.

### Everolimus

Long-term results from a phase 2 study of the oral mammalian target of rapamycin (mTOR) inhibitor everolimus (10 mg daily) showed at least PR in 50% (additional 23% minor responses [MRs]) of previously treated patients. Responses were rapid, occurring at a median of 2 months, and the median PFS was 21 months. Grade ≥3 toxicities occurred in 67% of patients. Among previously untreated patients (N = 33), everolimus induced at least PR in 61% (plus 12% MRs), although discordance between serum IgM levels and bone marrow disease burden was commonly observed. Six (18%) patients discontinued therapy due to toxicity. Myelosuppression with everolimus was common, and significant nonhematological toxicities included diarrhea, fatigue, and stomatitis (8-27%). Additionally, 5% to 15% developed pulmonary toxicity, frequently resulting in interruption or discontinuation of therapy. Everolimus...
may therefore be considered for selected patients with relapsed or refractory disease and limited options.

**Fludarabine**

Nucleoside analogs have been used extensively in the treatment of WM, either alone or in different combinations. In the large WM1 randomized phase 3 study, oral fludarabine was superior to chlorambucil in terms of response rates, PFS, and overall survival (OS) in newly diagnosed WM/lymphoplasmacytic lymphoma. Fludarabine has been studied in combination with rituximab, with or without cyclophosphamide (FR or FCR). Tedeschi et al. published long-term results (median follow-up, 37 months) with FCR in either previously untreated patients or patients relapsing after 1 line of alkylator-based (chlorambucil or cyclophosphamide) therapy. At least PR was observed in 74.4% (CR in 11.6% and VGPR in 20.9%), with an improvement of the quality of responses observed during follow-up, to a final 18.6% of CRs. Median event-free survival was 50 months, and estimated 4-year OS was 69%. Myelosuppression, especially neutropenia, was the main reason for treatment discontinuation, including episodes of long-lasting neutropenia after the end of treatment, whereas 3 patients developed myelodysplastic syndrome. In retrospective studies, fludarabine-based therapy was associated with an increased risk of secondary malignancies, although the frequency was not greater than with chlorambucil in the WM1 study. Nevertheless, response rates with fludarabine combinations are high, even in patients with relapsed or refractory WM, and the duration of response is long. Fludarabine-based combinations should be considered in patients with relapsed/refractory WM, with good performance status. In young patients who are autologous stem cell transplantation (ASCT) eligible, it is preferable that stem cells be collected before fludarabine administration.

**Oral alkylating agents**

Alkylators as single agents have been associated with relatively low rates and delayed responses. Single-agent chlorambucil may induce responses in up to 40% of patients; however, the randomized WM1 study indicated that chlorambucil is inferior to single-agent oral fludarabine.

**Immunomodulatory drugs**

Thalidomide has clinical activity in pretreated or previously untreated patients with WM, either alone or with rituximab. Primary therapy with thalidomide/rituximab induced PRs in 70%, and the median time to progression was 35 months. However, doses up to 200 mg/day were poorly tolerated (mainly due to neurotoxicity). Because of the advanced age of many patients (who are less tolerant to thalidomide) and the coexistence of WM-related neuropathy, thalidomide is not a primary choice. Nevertheless, the minimal myelotoxicity of thalidomide may be important for selected patients with severe cytopenias (especially those with severe thrombocytopenia). Lenalidomide with rituximab may be affected by polymorphisms in the Fc-γ-III receptor.

**Monoclonal antibody therapy**

**Rituximab.** Single-agent rituximab is moderately active (responses rates of ~30%); more extended administration is associated with higher response rates. Rituximab-based combinations (with alkylating agents, nucleoside analogs, proteasome inhibitors, and immunomodulatory drugs) are the mainstay of WM therapy. Rituximab has a favorable toxicity profile and is neither myelospressive nor stem cell toxic. However, rituximab is associated with a potentially clinically significant complication, IgM flare: this surge of IgM levels may be observed with either single-agent rituximab or with rituximab combinations with alkylating agents, nucleoside analogs, or proteasome inhibitors (bortezomib or carfilzomib), and has also been observed with other monoclonal anti-CD20 antibodies (such as ofatumumab). IgM flare may require immediate institution of plasmapheresis. Furthermore, response to rituximab may be affected by polymorphisms in the Fc-γ-III receptor.

Dimopoulos et al. reported updated results of the DRC regimen phase 3 study with a minimum follow-up of >6 years. Median PFS was 35 months, and median time to next treatment was 51 months. Forty patients received second-line treatment, 28 (70%) patients were retreated with either rituximab alone or rituximab-based regimens, and 82% achieved at least MR. Thirty-five (49%) patients died (including 15 patients from unrelated causes). One patient, who received further therapy with fludarabine, developed myelodysplastic syndrome, and 2 patients developed diffuse large B-cell lymphoma. Five-year OS was 62%, and median OS was 95 months.

Rituximab maintenance improves duration of response in patients with other low-grade lymphomas, especially follicular lymphoma. A retrospective comparison indicated that maintenance rituximab may improve quality of responses and prolong PFS and time to next therapy in both previously untreated and pretreated WM patients, although at the expense of increased infections (mainly grade ≥ 2). An ongoing prospective, randomized study examines the impact of maintenance rituximab following BR. Due to the lack of prospective data, the use of maintenance rituximab is not routinely recommended.

**Ofatumumab.** Ofatumumab is a fully human monoclonal anti-CD20 antibody approved for the treatment of patients with chronic lymphocytic leukemia. Ofatumumab was given to 37 patients (28 with relapsed/refractory and 9 with untreated WM) at 2 dose levels (4 weekly infusions of 1000 vs 2000 mg) following
a dose of 300 mg on the first week: nonprogressing patients received a second cycle at week 16. After the first cycle, 11 (30%) achieved PR and 7 (19%) achieved MR; 12 patients received a second cycle. The percentage of those with at least MR after both cycles was 59% (PR in 38%), which was somewhat higher with higher doses (47% vs 68%) and in therapy-naive (6/9, 67%) and rituximab-naive (9/12, 75%) patients compared with rituximab-exposed patients (13/25, 52%). Infusion-related reactions were common, especially during the first dose; mild infusions were also common, and IgM flare was observed. Ofatumumab has promising activity, may be active in patients with prior exposure to rituximab, and may be considered for patients intolerant to rituximab; however, more data are needed in rituximab-refractory disease. Combinations of ofatumumab with other agents in WM are under investigation.

**Alemtuzumab.** CD52 is highly expressed in lymphoplasmacytic cells; however, the toxicity of the anti-CD52 antibody alemtuzumab is high, especially infectious complications, most notably cytomegalovirus reactivation. Results after long follow up (median follow-up, 64 months) from 28 patients (23 previously treated and 12 [46%] refractory to the most recent therapy) indicated the activity of alemtuzumab (at least PR in 36% and at least MR in 39%; median time to progression, 14.5 months)44 from 28 patients (23 previously treated and 12 [46%] refractory to the most recent therapy) indicated the activity of alemtuzumab (at least PR in 36% and at least MR in 39%; median time to progression, 14.5 months) but toxicity was significant, including deaths of patients while on therapy. Cytomegalovirus reactivation occurred in 18%, and new-onset autoimmune thrombocytopenia occurred in 4 (14%) patients. Based on the above results, the toxicity of the drug must be weighed against available treatment options and on an individual and restrictive basis.

**Management of newly diagnosed patients who require therapy for WM**

The data on therapy of WM come mainly from nonrandomized studies because only few randomized studies have been conducted in the field. Based on the available data, as well as the experience from the treatment of patients with low-grade lymphomas, specific recommendations can be made based on individual patient needs (Tables 3 and 4).

**Patients with WM-related cytopenias or organomegaly or bulky lymphadenopathy**

Most patients with WM require therapy because of cytopenias, most commonly anemia, and/or organomegaly with or without constitutional symptoms. Toxicity and efficacy are very important considerations. Rituximab-based combinations are recommended for patients with moderate to severe symptomatology. Rituximab in combination with cyclophosphamide and steroids (DRC45) or bendamustine (BR) are primary options. When rapid disease control is needed (as in patients with bulky symptomatic lymphadenopathy), BR or fludarabine/rituximab combinations may be considered. However, given the increased toxicity (early and late) of nucleoside analogs and the potential impact on stem cell collection, their use should be avoided in most, especially in younger patients.

**Patients with symptomatic hyperviscosity, cryoglobulinemia, or cold agglutinemia**

Morbidity due to paraprotein-mediated hyperviscosity, cryoglobulinemia, or cold agglutinemia is common. Rituximab-associated IgM flare may worsen paraprotein-related symptoms. Plasmapheresis should be considered for patients with symptomatic hyperviscosity and/or severe cryoglobulinemia and cold agglutinemia. Preemptive plasmapheresis before rituximab may be considered for patients with IgM ≥ 4 g/dL to avoid symptomatic IgM flare. In patients without symptomatic hyperviscosity, bortezomib may rapidly reduce IgM levels; induction with single-agent bortezomib can be considered before institution of rituximab (as in BDR).29 Weekly and/or subcutaneous administration of bortezomib is preferred. In patients at high risk for neuropathy, bendamustine can be considered; FCR is very effective but toxic. For patients with cold agglutinin disease requiring therapy, the fludarabine/rituximab combination is superior over rituximab alone46; however, toxicity should be weighed against combinations such as DRC, BDR, or bendamustine/rituximab.

**Patients with paraprotein-related neuropathy**

The treatment of IgM-related neuropathy may initially involve a course of plasmapheresis, particularly in patients with an aggressive course of progressing neuropathy. Plasmapheresis should not be used as a permanent modality. Systemic chemotherapy with rituximab resulted in improvement in sensory function in several studies, including a placebo-controlled trial.47 Single-agent rituximab can be considered as the first intervention in patients with mild, slowly progressive neuropathy. In patients with moderate to severe IgM-related neuropathy, data indicate more rapid improvement with the fludarabine-rituximab combination than with rituximab alone.48 Thus, in patients with more severe or a more aggressive course of IgM neuropathy, a rituximab-based combination appears reasonable. Fludarabine-rituximab is effective but toxic, and DRC is safe; bendamustine/rituximab may achieve robust paraprotein reductions, but there is limited experience in IgM-related neuropathy.
Patients who experience a rituximab-related IgM flare may also develop a flare in their neuropathy. Symptomatic treatment should also be considered (ie, with gabapentin, pregabalin, and duloxetine).\(^{49}\) Bing-Neel syndrome is a rare complication of WM characterized by direct infiltration of the central nervous system by malignant cells with or without cerebrospinal fluid hyperglobulinemia. There are limited reports on the management of these patients with aggressive chemotherapy, which may also require intrathecal therapy.\(^{50,51}\)

**Patients with IgM-associated amyloidosis**

IgM-associated light chain (AL) amyloidosis is a rare condition with distinctive clinical characteristics.\(^{52,53}\) These patients are fragile due to systemic amyloid organ involvement and require a dedicated approach. Treatment should aim at the rapid elimination of the amyloidogenic light chains, with monitoring of the free light chains and cardiac biomarkers. There is limited evidence on the applicability and outcome of treatment with regimens designed for WM to IgM-AL amyloidosis.\(^{52-56}\) In selected patients, ASCT may be considered. Given the activity in patients with non-IgM AL amyloidosis and in WM, bortezomib-based therapy could be used in carefully selected patients.\(^{59,56}\)

**Salvage therapy**

The panel encourages the participation of patients with relapsed or refractory WM in clinical trials exploring novel agents or strategies. Outside clinical trials, treatment options depend on the duration and response to prior therapies, the patient’s overall condition and age, and candidacy for ASCT.

Administering the same regimen used for primary treatment is reasonable in patients who achieved responses that lasted \(\geq 12\) months; otherwise, use of an alternate single agent or combination is recommended. Updated results from the phase 2 DRC study indicate that this is an effective strategy for many patients.\(^{46}\)

For patients with short-lasting remissions (<12 months) or with progressive disease/resistance to a first-line regimen, second-line treatment should include agents of a different class, either alone or in combination. Exposure to stem cell-damaging agents should be avoided in patients who are candidates for ASCT, especially if stem cells have not been harvested.

All regimens discussed under primary treatment options are effective salvage therapies. Bortezomib in combination with rituximab and/or dexamethasone is reasonable, but neurotoxicity is of concern. Bendamustine-based therapy is effective mostly in combination with rituximab. FCR is effective but toxic. Ofatumumab for rituximab-intolerant or -resistant patients may be considered. Everolimus or alemtuzumab may be considered for selected patients with very limited treatment options, which should be followed closely for toxicity.

**SCT for patients with WM**

High-dose therapy with ASCT is an option for salvage therapy in selected patients with chemosensitive disease; patients with several lines of prior therapies (\(\geq 3\) lines) appear to have limited benefit from ASCT.\(^{57}\) As part of primary therapy, ASCT could be considered in selected young patients with high risk IPSSWM and elevated lactate dehydrogenase. The use of myeloablative or nonmyeloablative allogeneic SCT is less defined. Younger patients with slowly progressing disease may be better candidates for allo-SCT. However, in view of the increasing treatment options and the high morbidity and mortality associated with allo-SCT, the opinion of the panel is that this therapy should preferably be considered in the context of a clinical trial.

**Management of patients intolerant to rituximab**

Rituximab is a chimeric (mouse/human) monoclonal antibody and may be intolerable in some patients, mainly due to major infusions reactions. Ofatumumab is a fully human monoclonal antibody and has been successfully administered in patients with prior rituximab-resistant disease and in patients intolerant to rituximab. IgM flare is also observed with ofatumumab; therefore, similar precautions as with rituximab should be considered.

**Future perspectives**

The identification of the common somatic mutation in MyD88 offered the opportunity for a more targeted approach. This mutation results in tonic MYD88-IRAK signaling, which activates the nuclear factor-\(\kappa\)B and mitogen-activated protein kinase pathways to support growth and survival of WM cells. Bruton’s tyrosine kinase (BTK) has a critical place in signaling transduction through this signaling pathway,\(^{58}\) and ibrutinib, a selective BTK inhibitor, has shown high activity in MyD88-mutated cell lines and very promising results in patients with relapsed/refractory WM. Recently, ibrutinib was approved for the treatment of patients with relapsed or refractory mantle cell lymphoma or chronic lymphocytic leukemia. Ixazomib is an orally available proteasome inhibitor that has shown efficacy in myeloma patients and is under investigation in phase 1/2 studies in relapsed/refractory WM. Oprozomib, an orally available epoxysketone class proteasome inhibitor, is under investigation in myeloma and in WM. Obinutuzumab (GA-101) a new monoclonal anti-CD20 antibody, was recently approved for the treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil. A phase 3 study is comparing chemotherapy (CHOP) plus obinutuzumab or rituximab followed by maintenance with obinutuzumab or rituximab in patients with advanced untreated indolent non-Hodgkin’s lymphoma, including WM. The histone deacetylase inhibitor panobinostat showed activity in patients with relapsed/refractory WM, indicating a potential role for histone deacetylase inhibition in WM.\(^{39}\)

An important advancement is the initiation of phase 3 studies designed specifically for patients with WM, either in newly diagnosed or in the relapsed/refractory setting, through multicenter collaborations such as the European WM Consortium. Such studies will define the treatment strategies based on high-quality data and offer the opportunity of high-quality translational research.

**Authorship**

Contribution: M.D., E.K., and S.P.T. drafted the first version of the manuscript; and all authors reviewed the manuscript, provided comments and suggestions, and approved the final manuscript.

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