Treatment Recommendations for Waldenström Macroglobulinemia from the Eighth International Workshop on WM.


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**Keypoints:**

- Chemo-immunotherapy combinations provide durable responses, and are still indicated in most WM patients.
- Ibrutinib represents a novel and effective treatment option for symptomatic WM patients.

**Abstract**

Waldenström's 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 the International Workshops on WM (IWWM). At IWWM-8, a task force for treatment recommendations was empanelled to review recently published and ongoing clinical trial data, as well as impact of new mutations (MYD88, CXCR4) on treatment decisions, indications for B-cell receptor (BCR) and proteasome inhibitors, and future clinical trial initiatives for WM patients. The panel concluded that therapeutic strategies in WM should be based on individual patient and disease characteristics. Chemo-immunotherapy combinations with rituximab (R) and cyclophosphamide/dexamethasone (DRC), or bendamustine (Benda-R) or bortezomib/dexamethasone (BDR) provide durable responses, and are still indicated in most patients. The approval of the BTK-inhibitor ibrutinib in the US and in Europe represents a novel and effective treatment option for both treatment–naïve and relapsing patients. Other BCR-inhibitors, second-generation proteasome inhibitors (e.g. carfilzomib) and mTOR inhibitors are promising and may expand future treatment options. Active enrollment in clinical trials whenever possible was endorsed by the panel for most patients with WM.
Introduction

Waldenström's macroglobulinemia (WM) is a lymphoplasmacytic lymphoma in which the bone marrow (BM) is infiltrated by IgM-producing clonal lymphoplasmacytic cells (1). At the Second International Workshop on WM (IWWM-2), criteria for the clinico-pathological diagnosis of WM, as well as indications for initiation of therapy in WM were developed (2,3). IWWM consensus panels have since provided updated treatment recommendations (4-7). As part of IWWM-8, a consensus panel was formed to consider data from recent trials with novel agents and combinations. The updated recommendations for symptomatic untreated (Table 1) and previously treated (Table 2) are presented in this report.

Treatment indications

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-8) include IgM related complications and/or symptoms related to direct tumor cells BM involvement such as cytopenias, constitutional symptoms and bulky extramedullary disease. Some symptoms that need urgent therapy such as symptomatic hyperviscosity, moderate to severe hemolytic anemia, and symptomatic cryoglobulinemia. For patients who do not fulfill the criteria, and in whom only laboratory evidence may indicate a possible development of progressive disease (such as a minor decrease in hemoglobin level with asymptomatic anemia or mild increases in IgM) or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient, close observation is recommended (3).

Treatment Options

Due to the rarity of WM, treatments have been adopted from data derived from phase 2 studies, and more rarely from randomized experiences that have included only WM patients, or other indolent B-cell malignancies (8,9) More recently, a large randomized phase 3 study was undertaken to accelerate the study of ibrutinib in WM patients that met its accrual goal in less than 2 years (NCT02165397). The efficacy and toxicity of phase II and III studies in WM are summarized in Table 3.

Monoclonal antibodies as a single agent

Rituximab
Rituximab is widely used in WM patients, due to single agent as well as combination studies in WM patients as well as other indolent B cell malignancies. Anti-CD20 monoclonal antibody therapy alone or in combination with chemotherapy is an important standard of care for most patients with WM (7, 10-13). Two schedules for rituximab monotherapy have been studied in for WM: the standard one, in which one weekly infusion of 375 mg/m2 is administered for 4 weeks, and the extended one, in which responsive patients received 4 more weekly infusions during weeks 12-16. With the standard schedule of rituximab administration, the overall response rates (ORR) were 30-60%, and major responses were observed in 25-30% of patients. The durations of response (DOR) were 8-11 months in both untreated and previously treated patients in these studies (14,15). Even for patients with minor response, an improvement in hemoglobin and platelet counts, as well as a reduction in lymphadenopathy and splenomegaly can be observed with rituximab. With the extended rituximab schedule, the ORR is 35-45% and the DOR has exceeded 16-29 months (16,). Rituximab is well tolerated though in about 50% of patients, a transient increase in serum IgM levels (IgM flare) occurs (17). The rituximab induced IgM flare occurs mostly during the first months of treatment, but may persist for several months. This phenomenon is not associated with a higher risk of treatment failure, but physicians should be cautious not to interpret this phenomenon hastily as lack of response or even progression. In patients with baseline high serum IgM levels, the IgM flare can lead to hyperviscosity related complications (18). WM patients with high IgM levels (i.e. 4,000 mg/dL or higher) should undergo prophylactic plasmapheresis, or rituximab should be avoided during the first one or two courses of systemic therapy until IgM levels decline to a safer level (18,19). Late-onset neutropenia (LON) has also been described with rituximab, mostly when combined with chemotherapy (20). The underlying mechanism of LON is not understood, but a cellular immune mechanism and/or antibody-mediated complement cytotoxicity have been proposed (21). An association between a specific polymorphism in the immunoglobulin G Fc receptor (FcγRIIIa-V158/i2) and LON has been described (22).

Ofatumumab

Ofatumumab is a fully-human CD20-directed monoclonal antibody that targets a CD20-region at a different epitope than that of rituximab. Furman et al (23) studied ofatumumab as a monotherapy in 37 treatment naïve or previously treated patients. Ofatumumab was given at 300 mg in week 1, followed by either 1000 mg/week (low dose) or 2000 mg/week (high dose) during weeks 2-4. Patients with stable disease or a minor response at week 16 were eligible to receive a re-dosing cycle consisting of ofatumumab at 300 mg in week 1, then 2000 mg/week for 4 weeks. The ORR
was 59%, which included major responses in 35% of patients. The ORR was higher in rituximab-naive patients, and those with a serum IgM level of <4,000 mg/dL in the low-dose, but not high dose ofatumumab cohort. Two patients with serum IgM levels >4,000 mg/dL required plasmapheresis for renal insufficiency and hyperviscosity syndrome, and two patients experienced an IgM flare who subsequently responded. In patients with intolerance to rituximab, ofatumumab may represent a potential therapeutic option (24). A therapeutic test dose with appropriate prophylaxis should be considered prior to administration of ofatumumab in a patient with rituximab intolerance (24).

Combinations with Rituximab

Because rituximab is an active and non-myelosuppressive agent, its combination with various chemotherapeutic agents has been explored in WM. The choice of chemotherapy depends on the comorbidities, how fast disease control is required, and the manifestations of the disease.

Rituximab with Alkylators

The combination of dexamethasone, rituximab and cyclophosphamide (DRC) was evaluated in a prospective study of 72 untreated WM patients. An ORR of 83% was observed including 7% complete and 67% partial responses. The 2-year PFS was 67% for all evaluable patients, and 80% for responders. Median time to response was long (4.1 months) suggesting that this combination is not appropriate if rapid control of disease is necessary. Toxicities were mild, with only 9% grade 3/4 neutropenia (25). This study was recently updated, showing a time to treatment failure of 35 months. The majority of relapsing patients were still sensitive to rituximab-based therapies and long-term toxicity profile was favorable with only one case of MDS, and two cases of transformation to DLBCL. The cause of death was prospectively evaluated in this study, and only 32% of deaths were related to WM at a median of follow-up of 8 years. The 8-year OS based on IPSSWM score was 100%, 55% and 27% for low, intermediate or high-risk disease, respectively (p=0.005) (25,26).

Rituximab with Purine Analogues

Most data on fludarabine–based regimens have been discussed in previous consensus guidelines, and include fludarabine and rituximab combinations (5-7). Both rituximab and fludarabine (FR), as well as rituximab, fludarabine and cyclophosphamide (FCR) are effective as primary therapy, and salvage therapy with median progression-free survivals (PFS) exceeding 50 months (27-30). However, due to the risk of long lasting cytopenias as well as secondary malignancies with these
combinations, first line treatment use is not recommended, but could be an option in patients with high-risk relapsing disease.

Rituximab with Bendamustine

Rituximab and bendamustine (Benda-R) was compared to R-CHOP in a phase 3 open-label trial. A total of 546 patients were enrolled in this study for indolent NHL patients, including 41 patients with WM (22 treated with Benda-R and 19 with R-CHOP). Patients on the Benda-R arm received 6 cycles of bendamustine at 90 mg/m² on days 1, 2 and rituximab at 375 mg/m² on day 1 every 4 weeks. A similar ORR (95%) but with a longer PFS was reported for the Benda-R arm (median 69.5 months) versus CHOP-R (median 28.1 months), along with a better tolerance (lower rates of grade 3/4 neutropenia, infectious complications, peripheral neuropathies, and alopecia) (8).

The outcome of 30 WM patients with relapsed/refractory disease who received bendamustine alone, or with a CD20-directed antibody has also been examined (31). An ORR of 83% and a median PFS of 13 months was reported in this study. Overall, therapy was well tolerated though prolonged myelosuppression occurred in patients who had received prior nucleoside analogue therapy. Tedeschi et al (32) reported a retrospective study of Benda-R in 71 previously treated WM patients who received bendamustine at 50-90 mg/m² on days 1 and 2, with rituximab given on day 1. The ORR was 80%, and 75% of patients achieved a major response. Major toxicity was grade 3/4 neutropenia that occurred in 13% of courses. The median PFS was not reached after a median follow-up of 19 months. Among responders, the median time to 50% reduction in serum paraprotein was 3 months. No IgM flare was observed in this series. Sixty-six percent of patients completed the planned 6 courses. Ten patients discontinued due to toxicity. None of the patients developed aggressive lymphoma or secondary myelodysplastic syndrome/acute myeloid leukemia, but in 3 cases, a solid cancer was observed.

Rituximab plus Bortezomib

The Waldenstrom’s Macroglobulinemia Clinical Trials Group (WMCTG) studied bortezomib, dexamethasone and rituximab (BDR) in 23 untreated patients, with administration of intravenous bortezomib at 1.3 mg/m² and dexamethasone 40 mg twice a week at day 1, 4, 8, 11, and rituximab 375 mg/m² at day 11, for 4 cycles as induction treatment, and 4 more cycles at 3 months as maintenance treatment (33). The ORR and major response rates were 96% and 83% respectively, with a median time to response of 1.4 months. Sixty percent of patients discontinued treatment after 4 cycles because of treatment-related peripheral neuropathy. The median PFS was 66
months (34). Treatment with once a week bortezomib has also been investigated. Twenty-six patients received bortezomib at 1.6 mg/m² intravenously at day 1, 8 and 15 during 6 cycles, in a 28-day cycle, and rituximab 375 mg/m² at each cycle during 4 cycles (35). Eighty-eight percent of patients obtained a response, including 65% major response rate. The 1-year event free survival was 79%. Neurologic complications were limited, and no grade 3/4 treatment-related neuropathy was reported. Grade 3/4 neutropenia was observed in 12% of patients. Among previously treated patients with this regimen, the ORR was 81%, with 51% major response rate and a median PFS of 15.6 months. Sixteen percent of patients developed grade 3 neutropenia, and grade 3 neuropathy occurred in 5% of patients (36). Dimopoulos et al (37) reported the efficacy and toxicity of BDR in 59 treatment-naïve patients. In order to avoid “IgM flare” the first induction cycle consisted of bortezomib (1.3 mg/m² IV on days 1, 4, 8, 11), followed by four cycles of weekly bortezomib (1.6 mg/m² IV for 4 weeks) with rituximab and dexamethasone in cycles 2 and 5. Peripheral neuropathy was observed in 46% of the patients (grade ≥3 in 7%) but only 5 (8%) discontinued bortezomib due to neuropathy. After a minimum follow-up of 32 months, the median progression-free survival was 42 months, 3-year duration of response for patients with PR was 70%, and 3-year survival was 81%.

In the previous IWWM recommendations, the panel noted “neurotoxicity is the major concern with bortezomib because of underlying IgM-related neuropathy due to WM, or age-related co-morbidities such as diabetes. Weekly dosing and subcutaneous administration (as observed in myeloma patients) may reduce rates and severity of neuropathy, and is being explored in a randomised phase II trial of subcutaneous bortezomib, cyclophosphamide, rituximab versus fludarabine, cyclophosphamide, rituximab for initial therapy of WM (NCT01592981). The impact of the addition of subcutaneous bortezomib to DRC is also being evaluated in a large European phase III study (NCT01788020). 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 for WM patients receiving proteasome inhibitors.

Rituximab plus Carfilzomib

Carfilzomib, a second-generation proteasome inhibitor, is associated with a low risk of neurotoxicity in multiple myeloma (MM) patients and was recently evaluated in combination with rituximab and dexamethasone (CaRD), mainly in untreated WM patients (38). The schedule of carfilzomib was attenuated (days 1, 2 & 8 and 9) compared to myeloma dosing, and maintenance therapy (days 1, 2 only) was given every 8 weeks for 8 cycles. Overall response rate was 87%
(≥VGPR in 35%) and was not impacted by MYD88 or CXCR4 mutation status, and no grade ≥3 neuropathy was observed. With a median follow-up of 15.4 months, 20/31 (65%) patients remain progression-free. Carfilzomib is currently accessible in the United States as an off-label indication for WM, and on treatment options by the NCCN. However, it is not currently available for WM in many other countries.

**Maintenance Rituximab**

The role of maintenance therapy was addressed in a retrospective series of 248 rituximab-naïve WM patients who responded to a rituximab-containing regimen (35). Eighty-six patients (35%) of these patients subsequently received maintenance rituximab. Maintenance treatment with rituximab appeared to extend PFS and OS in comparison to those patients who were observed, though increased incidence of sinobronchial infections (mainly grade 1,2) along with depletion of uninvolved immunoglobulins (IgA, IgG) was observed with maintenance therapy (39). A randomized prospective study is ongoing in Germany (MAINTAIN study, NCT00877214), and is evaluating the impact of 2-years of rituximab maintenance versus observation alone after induction with rituximab and bendamustine in untreated patients.

**Stem cell transplantation (SCT)**

SCT (stem cell transplantation) remains an option for salvage therapy in WM, particularly among younger patients who have had multiple relapses or with primary refractory disease. In an European Bone Marrow Transplant Registry (EBMTR) study including 155 evaluable WM patients that underwent autologous stem cell transplantation (ASCT), the 5-year OS was 69%, PFS was 49%, the incidence of relapse (IR) was 47%, and the non-relapse mortality (NRM) was 5.6% (40). IR was significantly lower in patients receiving ASCT in first response (CR1, VGPR1, PR1) compared to transplantation in subsequent complete or partial responses or with refractory disease (39% vs 53%; p=0.001), translating into a significant DFS (50% vs 40%, p= 0.004) and OS benefit (71% vs 63%; p= 0.033) for the patients transplanted early in the course of their disease. The outcome of previously treated WM patients who received myelo-ablative and reduced-intensity allogeneic transplantation was also reported by the EBMTR (41). The ORR was 76%, and 5-year PFS and OS rates were 56% and 62%, respectively. Among patients who received reduced-intensity allogeneic transplantation, similar PFS and OS rates were observed (49% and 64%, respectively). Non-relapse mortality at 3 years was high at 33% and 23% for myeloablative and reduced-intensity allogeneic transplantation, respectively. Complete responses occurred in about 20% of patients with allogeneic HCT.
**Novel Treatment Agents**

**Immunomodulatory Agents**

In a phase I/II study lenalidomide monotherapy was used at low dose (starting at 15 mg) (trial RV-WM-0426) in 17 previously treated patients (42). At the highest dose tested, 20 mg, dose limiting toxicities occurred thus the dose of lenalidomide chosen for further testing was 15 mg/day for 21 days out of 28. Seven out of 14 (50%) patients completed one year of single agent lenalidomide treatment at 15 mg/day. In an intent-to-treat analysis, single agent lenalidomide provided an ORR of 29%. Interestingly, all responses were obtained from cycles 9-12. An IgM flare effect was observed in 3 patients. With a median follow-up of 36 months, the median TTP was 16 months and the 5-year OS was 91%. The most frequent adverse events (≥ grade 3) at 15 mg were 14% anemia and 43% neutropenia; no grade 3 thrombocytopenia was reported. The combination of rituximab and lenalidomide (25 mg daily for 3 weeks followed by 1 week rest) was studied by the WMCTG (43) in 16 WM patients, 12 of whom were previously untreated. The ORR was 50%, and only 1 case of neuropathy was observed. Abrupt decreases in hematocrit were observed in 88% of patients, and occurred despite reduction of lenalidomide to 5 mg/day. IgM flare was also observed, and necessitated plasmapheresis in some patients.

The combination of pomalidomide, dexamethasone and rituximab (PDR) was also explored in previously treated WM patients in a dose escalating Phase I study (44). Among the 7 enrolled patients, 3 (43%) attained a major response. The median time to response was 2.1 months. Three patients required emergent plasmapheresis for an IgM flare, and led to discontinuance of protocol therapy. The median response duration was 15.1 months, and all 3 patients continued to respond at study reporting.

**mTOR Inhibitors**

Ghobrial et al (45) reported the long–term results of a phase II trial with everolimus in 60 relapsed/refractory patients. The response rate was 50% of PR and 23% of MR. The median time to response was 2 months and the median PFS was 21 months. Toxicity was hematologic with 27% and 20% of grade 3-4 anemia and thrombocytopenia. Pulmonary toxicity was also reported. Among untreated, symptomatic WM patients, the overall and major response rates for everolimus are 72% and 60%, respectively (46). Discordance between serum IgM levels and BM disease response were common and complicated response assessment. Oral ulcerations frequently occur with everolimus, and an oral dexamethasone swish and spit solution may be preventative. Toxicity
with everolimus was pronounced in this study, and included cytopenias and pulmonary pneumonitis requiring frequent dose reductions. The results of a phase I/II of everolimus in combination with rituximab with or without bortezomib in 46 patients was recently reported (47). The response rate was 89% and the median progression-free survival was 21 months in 36 patients who received full dose therapy. Everolimus is currently accessible in the United States as an off-label indication for WM, and on treatment options by the NCCN. However, it is not currently available for the WM in many other countries.

**B-Cell Receptor (BCR) pathway inhibitors**

Ibrutinib is a BTK inhibitor effective in high-risk CLL and in mantle cell lymphoma patients. There is a strong rationale to use this drug in WM patients given that BTK is activated by mutated MYD88, and enhances the survival of WM cells by activation of NFkB. Treon et al (48) recently reported the results of a prospective study of ibrutinib in 63 symptomatic patients with WM who received at least one previous treatment. The median time to at least a minor response was 4 weeks. The ORR was 91%, and the major response rate was 73%. The median time to at least a minor response was 4 weeks, and the estimated 2-year PFS and OS rates among all patients were 69% and 95%, respectively. Treatment-related toxic effects of grade 2 or higher included neutropenia (in 22% of the patients) and thrombocytopenia (in 14%), which were more common in heavily pretreated patients; post procedural bleeding (in 3%); epistaxis associated with the use of fish-oil supplements (in 3%); and atrial fibrillation associated with a history of arrhythmia (5%). The results of therapy with ibrutinib as a single agent are impressive and the high rates of response and tolerance to therapy were confirmed in a study of single agent ibrutinib in 31 relapsed/refractory WM patients by Dimopoulos et al (49) In addition, Furman et al (50) have reported on the durability of responses in previously treated WM patients included on a Phase I study who received 12.5 mg/kg/day to 560 mg a day of ibrutinib. Three of four WM patients included in this study achieved a major response, and continued to respond >4 years following start of ibrutinib therapy.

Overall treatment with ibrutinib is well tolerated in WM patients. An off target effect of ibrutinib on platelet aggregation with bleeding complications has been described in CLL trials (51). The use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Moreover, acquired von Willebrand disease (aVWD) associated with a high IgM level can be responsible for bleeding (52), though patients with aVWD showed benefit following ibrutinib (48). The panel recommends that testing for von Willebrand activity in patients with a
history of bleeding diathesis before starting ibrutinib is reasonable. In case of surgery, ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. Another potential off-target effect is the risk of atrial fibrillation. In a series of 112 WM patients on ibrutinib, the cumulative risk of atrial fibrillation at 1, 2, and 3 years was 5.4%, 7.1%, and 8.9%, respectively (53). Patients with a prior history of atrial fibrillation had a shorter time to atrial fibrillation compared to those without a history (3.9 versus 33.4 months, respectively). Nearly all patients who developed atrial fibrillation were able to continue ibrutinib following cardiological intervention and/or ibrutinib dose reduction (53). In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib can also be considered. Ibrutinib also produces a mild decrease in QT interval. Underlying mechanism and safety relevance of this finding are not known. Clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening of their QT interval. Randomized studies are ongoing comparing the efficacy of rituximab with either placebo or ibrutinib in relapsing and in treatment-naïve patients (NCT02165397). In chronic lymphocytic leukemia resistance to ibrutinib with BTK C481S mutation or PLCζ2 mutations have been described in few patients and remain under investigation (54).

Novel BTK inhibitors are in clinical development and may offer additional choices: CC-292, ONO-4059, ACP-196, BGB-3111. The cost-effectiveness of these new compounds will invariably need to be addressed through pharmacoeconomic studies.

Both MYD88 and CXCR4 mutations can impact overall and major responses to ibrutinib. WM patients who are wild-type for MYD88 had a lower ORR and no major response to ibrutinib (55). The efficacy of this drug may be also be impacted by CXCR4 mutations, with both lower ORR and major responses as well as delayed responses observed in WM patients with mutated CXCR4 (55). The panel recommends that testing for MYD88 can be considered for patients that are candidates for ibrutinib therapy, and that MYD88 and CXCR4 mutation status should be investigated in the context of clinical trials to clarify their impact on treatment outcome for novel agents. The panel also agrees that more data is needed for tailoring treatment options according to MYD88 and CXCR4 mutation status.

**Future Options**

**Which clinical trials should be prioritized in the front line setting for symptomatic WM patients?**
Many options are available in first line: chemo-immunotherapy with anti-CD20 monoclonal antibodies or the combination of anti-CD20 monoclonal antibodies with proteasome inhibitors. The aim of the first line treatments is to reach a high response rate with a prolonged PFS. The panel agrees there is need to perform clinical trials with chemotherapy-free combinations with new compounds alone or in combination with anti-CD20 antibodies. Ibrutinib is approved in the front-line setting and front line trials with ibrutinib and other BCR inhibitors are needed for assessing the efficacy and tolerability of these agents in treatment-naïve patients.

**Which clinical trials should be prioritized in the salvage setting for symptomatic WM patients?**

The panel agrees with prioritizing investigation of BCR- inhibitors along with existing and novel compounds in patients in relapsed/refractory setting. Combination with proteasome inhibitors would be of interest for overcoming resistance, interfering with the two key pathways that are affected by MYD88. A randomized trial comparing the efficacy of BCR inhibitors to that of BCR-inhibitors and proteasome inhibitors could answer this question. Obinutuzumab which has shown efficacy in CLL and follicular lymphoma is of interest as a combination partner in WM. The use of CXCR4 antagonists such as plerixafor or ulocuplomab, as well as other antagonists in development may offer an opportunity to extend the activity of therapeutics impacted by the CXCR4 mutation in WM patients.

**Summary**

Rituximab alone can be considered for WM patients with immunological disorders secondary to WM, such as anti-MAG neuropathy or in frail patients less likely to tolerate chemoimmunotherapy. Rituximab should be avoided, withheld, or plasmapheresis performed before rituximab is given in patients with high IgM levels due to concerns of an IgM flare, and prompting symptomatic hyperviscosity. Chemoimmunotherapy combinations with rituximab (R) and cyclophosphamide/dexamethasone (DRC), or bendamustine (Benda-R) or bortezomib/dexamethasone (BDR) provide durable responses, and are still indicated in most patients. The approval of the BTK-inhibitor ibrutinib in the US and in Europe represents a novel and effective treatment option for both treatment-naïve and relapsing patients. Other BCR-inhibitors, second-generation proteasome inhibitors (e.g carfilzomib) and mTOR inhibitors are promising and may
expand future treatment options. Active enrollment in clinical trials whenever possible was endorsed for most patients with WM.

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Authorship

All authors participated on consensus panel discussions that contributed to manuscript content and recommendations. VL, MAD, and SPT edited the final manuscript draft based on input from panel members.

Conflicts of interest


EK, speaker for Janssen Pharmaceuticals, Inc., Onyx Pharmaceuticals, Inc., Takeda Oncology, Inc.

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References


Table 1. Consensus updates on the management of symptomatic, untreated WM patients.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Plasmapheresis</strong></td>
<td>Plasmapheresis should always and immediately be used for patients with symptomatic hyperviscosity. Furthermore, plasmapheresis can be used to prevent flare in patients with high IgM level (typically &gt;4,000 mg/dL) prior to rituximab administration. Plasmapheresis alone is not an effective treatment of the disease and must be followed by a rapidly acting cytoreductive treatment.</td>
</tr>
<tr>
<td><strong>Rituximab as a single agent</strong></td>
<td>Because of the lower chance of response in WM patients with high IgM levels, and the risk of an IgM-flare, rituximab single agent therapy should be avoided in patients with high IgM levels, but rather considered for WM patients with immunological disorders secondary to WM, such as anti-MAG neuropathy or in frail patients less likely to tolerate chemoimmunotherapy.</td>
</tr>
<tr>
<td><strong>Dexamethasone, Rituximab, Cyclophosphamide (DRC)</strong></td>
<td>DRC is an active and safe treatment choice in first line for WM with a manageable toxicity, and can be considered in frail patients requiring combination therapy.</td>
</tr>
<tr>
<td><strong>Bendamustine, Rituximab (Benda-R)</strong></td>
<td>Benda-R is effective in treatment-naive WM patients. Treatment is well tolerated even in elderly patients with limited episodes of myelosuppression and infections when compared to purine analogues-based regimens. In elderly patients, as well as those with renal impairment, dose of bendamustine needs to be lowered. Four cycles of Benda-R may be sufficient to achieve adequate response in most WM patients.</td>
</tr>
<tr>
<td><strong>Bortezomib based therapy</strong></td>
<td>Primary therapy with bortezomib is recommended for patients with high IgM levels, symptomatic hyperviscosity, cryoglobulinemia or cold agglutininemia, amyloidosis and renal impairment, or in young patients in whom avoidance of alkylator or nucleoside analogue therapy is desired. The panel also recommends that bortezomib should ideally be given once weekly and possibly by subcutaneous route but, in case of urgent reduction of the IgM level, bortezomib can be started at a dose of twice a week for one or two cycles and then be changed to once weekly dosing in order to reduce risk of neurotoxicity.</td>
</tr>
<tr>
<td><strong>Carfilzomib based therapy</strong></td>
<td>Carfilzomib based therapy represents an emerging neuropathy-sparing option for proteasome-inhibitor based therapy for WM. Cardiac toxicity has been reported in 3-4% of MM patients and could be an issue especially in elderly WM patients with pre-existing cardiac conditions. Other open issues include the optimal dose of carfilzomib, and the optimal schedule of administration.</td>
</tr>
<tr>
<td><strong>Ibrutinib</strong></td>
<td>Ibrutinib is an option in symptomatic WM patients. Ibrutinib is approved as primary therapy in WM patients by the U.S. FDA, and Health Canada, and by the EMA as primary therapy in WM patients who are not candidates for chemo-immunotherapy. Ibrutinib should not be stopped unless toxicity or disease progression is suspected. Increases in serum IgM and reductions in hemoglobin can occur if ibrutinib is held, and should not be regarded as treatment failure. The optimal use of ibrutinib (i.e. in first line or previously treated disease), as a single agent or in combination continues to be a subject of investigation.</td>
</tr>
<tr>
<td><strong>Post-induction maintenance therapy</strong></td>
<td>Maintenance therapy with rituximab is an option in WM patients given the benefits observed in other indolent lymphomas, as well as the results from a retrospective outcome study, though confirmatory prospective data, as well as studies to address the optimal dose, schedule, and duration of maintenance rituximab are needed.</td>
</tr>
</tbody>
</table>
Table 2. Consensus updates on the management of symptomatic, previously treated WM patients.

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retreatment</strong></td>
</tr>
<tr>
<td>Treatment with any of the interventions listed for symptomatic, untreated patients can be considered for previously treated patients requiring therapy. Re-treatment may be considered with any of the above interventions if a response was achieved for 2 or more years with the prior regimen. Patients who progressed on frontline ibrutinib should not be retreated with ibrutinib.</td>
</tr>
<tr>
<td><strong>Ofatumumab</strong></td>
</tr>
<tr>
<td>In patients with intolerance to rituximab, ofatumumab is a potential therapeutic option.</td>
</tr>
<tr>
<td><strong>Ibrutinib</strong></td>
</tr>
<tr>
<td>Ibrutinib is an option in symptomatic WM patients. Ibrutinib is approved as primary therapy in WM patients by the U.S. FDA, and Health Canada, and by the EMA as primary therapy in WM patients who are not candidates for chemo-immunotherapy. Ibrutinib should not be stopped unless toxicity or disease progression is suspected. Increases in serum IgM and reductions in hemoglobin can occur if ibrutinib is held, and should not be regarded as treatment failure. The optimal use of ibrutinib (i.e. in first line or previously treated disease), as a single agent or in combination continues to be a subject of investigation.</td>
</tr>
<tr>
<td><strong>Nucleoside analogues</strong></td>
</tr>
<tr>
<td>Fludarabine-based combinations can be considered in fit WM patients with previously treated disease who have failed other, less toxic treatments. In young patients who are ASCT eligible, stem cells should be collected before fludarabine administration.</td>
</tr>
<tr>
<td><strong>Everolimus</strong></td>
</tr>
<tr>
<td>Everolimus can be considered as a treatment option in the relapsed or refractory setting, though owing to the toxicities associated with this agent, everolimus is best considered in patients who are unresponsive or progressed after multiple lines of other better tolerated therapies. Serial BM biopsies may help clarify underlying disease response or progression to everolimus given the IgM discordance observed with this agent.</td>
</tr>
<tr>
<td><strong>Immunomodulatory Agents</strong></td>
</tr>
<tr>
<td>Based on the current data, the use of lenalidomide and pomalidomide should be considered in the context of a clinical trial given their potential adverse events.</td>
</tr>
<tr>
<td><strong>Stem cell transplantation</strong></td>
</tr>
<tr>
<td>The panel agrees that SCT should be discussed in selected WM cases, though should take into account the numerous available alternative treatment options. ASCT is a feasible and effective treatment option for high risk transplant eligible WM patients, but should ideally be offered at early relapses. ASCT is not as beneficial for patients exposed to more than three line therapies or with chemorefractory disease. Allogeneic SCT, when appropriate, should preferably be considered in the context of clinical trials.</td>
</tr>
</tbody>
</table>
Table 3. Summary of efficacy and toxicity for select phase II and III studies of therapeutic regimens for Waldenstrom’s macroglobulinemia.

<table>
<thead>
<tr>
<th>Combination</th>
<th>N</th>
<th>Treatment naïve</th>
<th>ORR</th>
<th>Major RR</th>
<th>CR</th>
<th>Median TTP/PFS (months)</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>R + C + Dex (25,26)</td>
<td>72</td>
<td>100%</td>
<td>83%</td>
<td>74%</td>
<td>7%</td>
<td>35 (TTP)</td>
<td>Mild hematologic toxicity</td>
</tr>
<tr>
<td>R + F (27)</td>
<td>43</td>
<td>63%</td>
<td>95%</td>
<td>86%</td>
<td>4%</td>
<td>51 (TTP)</td>
<td>Hematologic toxicity, infection</td>
</tr>
<tr>
<td>R + F + C (28)</td>
<td>43</td>
<td>65%</td>
<td>79%</td>
<td>74%</td>
<td>11%</td>
<td>NR</td>
<td>Hematologic toxicity including prolonged cytopenias, infection, secondary malignancies</td>
</tr>
<tr>
<td>R+F+C (30)</td>
<td>82</td>
<td>33%</td>
<td>81%</td>
<td>74%</td>
<td>10%</td>
<td>79% at 3 y (PFS) 79 in relapse (PFS)</td>
<td>Hematologic toxicity including prolonged cytopenias, infection, secondary malignancies</td>
</tr>
<tr>
<td>R+F+C (29)</td>
<td>40</td>
<td>0%</td>
<td>80%</td>
<td>80%</td>
<td>10%</td>
<td>Median not reached at 52 (TTP)</td>
<td>Hematologic toxicity including prolonged cytopenias, infection, secondary malignancies</td>
</tr>
<tr>
<td>R+ Bendamustine (8)</td>
<td>22</td>
<td>100%</td>
<td>95%</td>
<td>NA</td>
<td>NA</td>
<td>69.5</td>
<td>Hematologic toxicity, rash, fatigue</td>
</tr>
<tr>
<td>R+ Bendamustine (32)</td>
<td>71</td>
<td>100%</td>
<td>80%</td>
<td>75%</td>
<td>7%</td>
<td>NR</td>
<td>Hematologic toxicity, rash, fatigue</td>
</tr>
<tr>
<td>R + Bort (35)</td>
<td>26</td>
<td>100%</td>
<td>88%</td>
<td>65%</td>
<td>4%</td>
<td>NR</td>
<td>IgM flare, nausea, decreased incidence of peripheral neuropathy with weekly bortezomib dosing</td>
</tr>
<tr>
<td>Regimen</td>
<td>ORR</td>
<td>Major RR</td>
<td>CR</td>
<td>NR</td>
<td>TTP</td>
<td>PFS</td>
<td>Toxicity</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
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<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>R + Bort + Dex (33, 34)</td>
<td>23%</td>
<td>100%</td>
<td>96%</td>
<td>83%</td>
<td>13%</td>
<td>66 (TTP)</td>
<td>Hematologic toxicity, high rate of peripheral neuropathy with twice weekly bortezomib dosing</td>
</tr>
<tr>
<td>R + Bort (36)</td>
<td>37%</td>
<td>0%</td>
<td>81%</td>
<td>51%</td>
<td>5%</td>
<td>16 (TTP) 15.6 (PFS)</td>
<td>IgM flare nausea, lymphopenia Low rate of peripheral neuropathy with weekly bortezomib dosing</td>
</tr>
<tr>
<td>R + Bort + Dex (37)</td>
<td>59%</td>
<td>100%</td>
<td>85%</td>
<td>68%</td>
<td>3%</td>
<td>42 (PFS)</td>
<td>Low rate of peripheral neuropathy with twice to once weekly bortezomib dosing after first cycle, IgM flare</td>
</tr>
<tr>
<td>Carfilzomib + R + Dex (I) (38)</td>
<td>31%</td>
<td>90%</td>
<td>87%</td>
<td>68%</td>
<td>3%</td>
<td>64% at 15months (TTP)</td>
<td>IgM flare, hypogammaglobulinemia, rare cardiomyopathy</td>
</tr>
<tr>
<td>R + Lenalidomide (I) (43)</td>
<td>16%</td>
<td>75%</td>
<td>50%</td>
<td>25%</td>
<td>0%</td>
<td>17 (TTP)</td>
<td>Hematologic toxicity, IgM flare</td>
</tr>
<tr>
<td>Everolimus (I) (45)</td>
<td>60%</td>
<td>0%</td>
<td>73%</td>
<td>50%</td>
<td>0%</td>
<td>25 (TTP) 21 (PFS)</td>
<td>Hematologic toxicity, stomatitis, pneumonitis, rash</td>
</tr>
<tr>
<td>Ibrutinib (47)</td>
<td>63%</td>
<td>0%</td>
<td>90.5%</td>
<td>73%</td>
<td>0%</td>
<td>69% at 2 years (PFS)</td>
<td>Bleeding, atrial fibrillation, mild hematologic toxicity</td>
</tr>
</tbody>
</table>

ORR, overall response rate; major RR, major response rate; CR, complete response rate; TTP, time to progression; PFS, progression free survival; NA, not available; NR, not reached. R, rituximab; F, fludarabine; C, cyclophosphamide; Bort, bortezomib; I, investigational outside United States.
Treatment recommendations for Waldenström macroglobulinemia from the Eighth International Workshop on WM