Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia

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Waldenström macroglobulinaemia is an indolent B-cell lymphoma with clearly defined criteria for diagnosis, initiation of therapy, and response, which was established by consensus panels at previous International Workshops for Waldenström Macroglobulinaemia (IWWM). The treatment options for Waldenström macroglobulinaemia continued to be researched after the publication of the eighth IWWM consensus recommendations in 2016, and at the tenth IWWM in New York, USA (October, 2018) an international consensus panel was formed to update treatment recommendations. Participants were selected as members of the consensus panel based on their expertise on Waldenström macroglobulinaemia. The initial live discussion took place during the tenth IWWM meeting and two separate teleconferences were held in June, 2019, and January, 2020, to refine recommendations. No external or financial support was received for the elaboration of these recommendations. According to these updated consensus recommendations, alkylating drugs (bendamustine, cyclophosphamide) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib), both in combination with rituximab, as well as BTK inhibitors (ibrutinib), alone or in combination with rituximab, are preferred first-line therapy options for symptomatic patients with Waldenström macroglobulinaemia. In previously treated patients with Waldenström macroglobulinaemia who had an initial durable response, reuse of a previous regimen or another primary therapy regimen are acceptable options. Novel BTK inhibitors (acalabrutinib, zanubrutinib, tirabrutinib) and the BCL2 antagonist venetoclax appear safe and active, and represent emerging options for the treatment of Waldenström macroglobulinaemia. The choice of therapy should be guided by the patient's clinical profile, genomic features, and drug availability.

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Introduction

Waldenström macroglobulinaemia is characterised by the malignant accumulation of IgM-secreting lymphoplasmacytic lymphoma cells in the bone marrow and other organs.[1] Since the initial development of treatment recommendations at the second International Workshop for Waldenström macroglobulinaemia (IWWM-2) in 2002,[2] treatment options for patients with Waldenström macroglobulinaemia have evolved, and treatment recommendations have been updated at subsequent workshops.[3–6] As part of the IWWM-10 (New York, NY, USA, Oct 11–13, 2018), a consensus panel was established to update the treatment recommendations for Waldenström macroglobulinaemia on the basis of the latest data from clinical trials.

Participants of the IWWM-10 were selected as members of the consensus panel depending on their expertise on Waldenström macroglobulinaemia and their participation in the discussions. The initial live open discussion took place during the actual IWWM-10 meeting in October, 2018, in New York. Following this meeting, two separate teleconferences (June, 2019, and January, 2020) were undertaken to further discuss and refine recommendations until consensus was reached. All consensus panel members participated in the live meeting and teleconferences. No external or financial support was received for the elaboration of these recommendations.

Treatment options

Anti-CD20 monoclonal antibody monotherapy

The chimeric anti-CD20 monoclonal antibody rituximab is the most commonly used monotherapy for the treatment of Waldenström macroglobulinaemia in the USA.[7] Rituximab monotherapy has been prospectively evaluated in several studies (table 1). Rituximab can induce IgM flares, which are rapid increases of serum IgM (≥25%) shortly after rituximab exposure and can occur in 50% of patients with Waldenström macroglobulinaemia who have rituximab monotherapy.[12,13] IgM flares occur more commonly with serum IgM concentrations greater than 4000 mg/dL and can worsen symptoms of hyperviscosity, neuropathy, cryoglobulinaemia, or cold agglutinin disease. IgM flares should not be considered as disease progression, because serum IgM concentrations can reduce following resolution of the flare, usually within 2–4 months. The panel recommends against rituximab monotherapy for patients with Waldenström macroglobulinaemia and serum IgM concentrations greater than 4000 mg/dL, whenever possible. Other rare adverse events associated with rituximab are rituximab intolerance and late onset neutropenia.[14,15] Management of late onset neutropenia should provide growth factor support and avoid additional exposure to rituximab. Rituximab intolerance is characterised by worsening infusion reactions that can cause rituximab therapy to become unsafe for the patients. For rituximab-intolerant

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	Drug	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)
Gertz et al[8]	Rituximab	34, 35 (n=69)	36 (52%)	19 (28%)	0	Median: 23 months (NR)
Treon et al[9]	Rituximab	12, 17 (n=29)	19 (66%)	14 (48%)	0	Median: 14 months (NR)
Dimopoulos et al[10]	Rituximab	34, 41 (n=75)	35 (47%)	24 (32%)	5 (7%)	30-month: 28% (NR)
Furman et al[11]	Ofatumumab	9, 28 (n=37)	22 (59%)	15 (41%)	0	Median: 18 months (14–22)

All studies reported adverse events of infusion reactions, infections, intolerance, and IgM flare. NR=not reported.

Table 1: **Selected anti-CD20 monotherapy regimens in patients with Waldenström macroglobulinemia**

	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)*
Laszlo et al[17]	Cladribine and rituximab	16, 13 (n=29)	26 (90%)	23 (79%)	7 (24%)	Median: not reached at 43 months (NR)
Treon et al[18]	Fludarabine and rituximab	27, 16 (n=43)	41 (95%)	37 (86%)	16 (37%)	Median: 51 months (NR)
Buske et al[19]	CHOP	25, 0 (n=25)	15 (60%)	NR	NR	Median: 22 months (NR)
Buske et al[19]	R-CHOP	23, 0 (n=23)	21 (91%)	NR	NR	Median: 63 months (NR)
Dimopoulos et al[20]	Cyclophosphamide, dexamethasone, and rituximab	72, 0 (n=72)	60 (83%)	53 (74%)	5 (7%)	Median: 35 months (NR)
Rummel et al[21]	Bendamustine and rituximab	19, 0 (n=19)	NR	NR	NR	Median: 70 months (IQR 37–73)
Rummel et al[21]	R-CHOP	22, 0 (n=22)	NR	NR	NR	Median: 28 months (IQR 18–51)
Rummel et al[22]	Bendamustine and rituximab	257, 0 (n=257)	236 (92%)	226 (88%)	10 (4%)	Median: 65 months (NR)

Adverse events have been reported for nucleoside analogues (cytopenias, infections, myeloid neoplasms), CHOP (neuropathy, alopecia, stomatitis), and bendamustine (rash, constipation). CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. NR=not reported. *95%CI unless otherwise specified.

Table 2: **Selected chemotherapy and rituximab combination regimens in patients with Waldenström macroglobulinemia**

patients, slow infusion rates should be tried and, if persistent, ofatumumab, a fully human monoclonal anti-CD20 antibody,[14] or other drugs could be considered. Ofatumumab might also be associated with lower rates of IgM flare.[11] There are no data on single-drug subcutaneous rituximab, obinutuzumab, or anti-CD20 biosimilars in patients with Waldenström macroglobulinaemia.

Chemoimmunotherapy

Chemoimmunotherapy combinations are the most commonly used regimens for Waldenström macroglobulinaemia treatment in Europe.[16] Chemotherapeutic drugs that have been evaluated prospectively in patients with Waldenström macroglobulinaemia include nucleoside analogues (ie, fludarabine and cladribine) and alkylating drugs (cyclophosphamide and bendamustine; table 2). The combination of nucleoside analogues and rituximab are highly active, with an overall response rate of 90–95% and very good partial response (VGPR) rates of 25–35%.[17,18] However, there is an increased risk of prolonged immunosuppression and myeloid neoplasms with these stem-cell toxic drugs, although the risk of secondary myeloid neoplasms was shown to be higher with chlorambucil than with fludarabine.[23] In another randomised study comparing treatment of 22 patients with indolent lymphomas (including Waldenström macroglobulinaemia) using rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) versus treatment of 19 patients using bendamustine and rituximab, there was higher incidence of alopecia, paresthesia, and stomatitis with R-CHOP, but higher incidence of skin rash and infections with bendamustine and rituximab.[21] No randomised studies have compared cyclophosphamide, dexamethasone, and rituximab (CDR) versus bendamustine and rituximab. However, two retrospective studies have suggested higher activity, but also higher toxicity, associated with bendamustine and rituximab versus CDR.[24,25]

Proteasome inhibitors in combination with rituximab

Bortezomib, carfilzomib, and ixazomib, all in combination with rituximab, have been shown in prospective studies to be effective for the treatment of patients with Waldenström macroglobulinaemia (table 3). A major concern with bortezomib, dexamethasone, and rituximab (BDR) treatment (bortezomib given intravenously twice a week) was an associated high rate of grade 3 (or worse) peripheral neuropathy reported in 7 (30%) of 23 patients

	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)	Adverse events
Treon et al[26]	Bortezomib, dexamethasone, and rituximab	23, 0 (n=23)	22 (96%)	19 (83%)	8 (35%)	Median: 66 months (NR)	Neuropathy, cytopenias, infections
Ghobrial et al[27]	Bortezomib (weekly) and rituximab	0, 37 (n=37)	30 (81%)	19 (51%)	2 (5%)	Median: 16 months (11–21)	Neuropathy, cytopenias, infections
Ghobrial et al[28]	Bortezomib (weekly) and rituximab	26, 0 (n=26)	23 (88%)	17 (65%)	2 (8%)	1-year: 75% (50–89)	Neuropathy, cytopenias, infections
Dimopoulos et al[29]	Bortezomib (weekly), dexamethasone, and rituximab	59, 0 (n=59)	50 (85%)	40 (68%)	6 (10%)	Median: 42 months (NR)	Neuropathy, cytopenias, infections
Treon et al[30]	Carfilzomib, dexamethasone, and rituximab	31, 0 (n=31)	27 (87%)	21 (68%)	11 (35%)	Median: 44 months (NR)	Hyperglycaemia, hyperlipasaemia, neutropenia
Castillo et al[31]	Ixazomib, dexamethasone, and rituximab	26, 0 (n=26)	25 (96%)	20 (77%)	4 (15%)	Median: not reached at 22 months (NR)	Infections, hyperglycaemia
Kersten et al[32]	Ixazomib, dexamethasone, and rituximab (subcutaneous)	0, 50 (n=50)	37 (74%)	26 (52%)	8 (16%)	Median: not reached at 20 months (NR)	Infections, hyperglycaemia

NR=not reported.

Table 3: **Selected proteasome inhibitor and rituximab combination regimens in patients with Waldenström macroglobulinaemia**

	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)
Treon et al[37]	Ibrutinib	0, 63 (n=63)	57 (90%)	50 (79%)	19 (30%)	5-year: 54% (95% CI 39–67%)
Dimopoulos et al[29]	Ibrutinib	0, 31 (n=31)	28 (90%)	22 (71%)	4 (13%)	18-month: 86% (66–94)
Treon et al[38]	Ibrutinib	30, 0 (n=30)	30 (100%)	25 (83%)	6 (20%)	18-month: 92% (73–98)
Dimopoulos et al[39]	Ibrutinib, rituximab	34, 41 (n=75)	70 (93%)	55 (73%)	20 (27%)	30-month: 82% (NR)
Owen et al[40]	Acalabrutinib	14, 92 (n=106)	99 (93%)	83 (78%)	8 (8%; IWWM-6) and 31 (29%; IWWM-3)	24-month: 90% (47–99, TN); 82% (72–89, RR)

All studies reported adverse events of cytopenia, bleeding, arrythmias, and hypertension. IWWM=International Workshop for Waldenström Macroglobulinaemia. NR=not reported. RR=relapsed or refractory. TN= treatment naive.

Table 4: **Selected BTK inhibitor-based regimens in patients with Waldenström macroglobulinaemia**

with Waldenström macroglobulinaemia.[26] Neuropathy prompted bortezomib therapy discontinuation in 14 (61%) of 23 patients. Weekly intravenous bortezomib regimens were associated with lower rates of grade 3 (or worse) neuropathy.[28,29,33,34] Therefore, regimens containing bortezomib should be used with caution in patients with Waldenström macroglobulinaemia and neuropathy. Subcutaneous administration of bortezomib is preferred, given a relatively low risk of neuropathy reported in patients with multiple myeloma.[35] Carfilzomib therapy has not been associated with neuropathy.[30] On the basis of a systematic review involving patients with multiple myeloma, carfilzomib was associated with an increased risk of cardiovascular events, which seems to be dose dependent, and should be used with caution in patients with Waldenström macroglobulinaemia and cardiovascular disease, particularly for patients older than 65 years.[36] Additionally, both bortezomib and carfilzomib are parenteral drugs, requiring at least weekly administration at an infusion centre. Ixazomib is taken orally and has not been associated with neuropathy or adverse cardiovascular events.[31] The safety and activity of subcutaneous rituximab, in combination with ixazomib and dexamethasone, was evaluated in a prospective study and appeared feasible and associated with relatively low incidence of infusion reactions.[32]

BTK inhibitors

BTK inhibition has shown to be highly active in patients with Waldenström macroglobulinaemia (table 4). The oral BTK inhibitor ibrutinib was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with symptomatic Waldenström macroglobulinaemia, following the results of a multicentre prospective phase 2 study in which 63 previously treated patients received ibrutinib (420 mg) orally once daily until disease progression or unacceptable toxicity.[37,39] Patients with Waldenström macroglobulinaemia who do not have *MYD88* mutations appeared to benefit the least from ibrutinib, because no patients attained major responses and all patients progressed within 2 years of therapy.[37] Additional studies on rituximab-refractory and

previously untreated patients have shown similar activity, supporting BTK inhibition as a treatment option for patients with Waldenström macroglobulinaemia.[38,42] Time to response, depth of response, and progression-free survival with ibrutinib monotherapy were shown to be adversely affected by *CXCR4* mutations, especially nonsense *CXCR4* mutations.[43]

The randomised phase 3 INNOVATE study[10] compared the response and survival outcomes of patients with Waldenström macroglobulinaemia who were treated with ibrutinib and rituximab versus placebo and rituximab. The combination of ibrutinib and rituximab was associated with faster time to response, higher rates of response, and improved progression-free survival than placebo and rituximab. On the basis of these results, the FDA and EMA approved ibrutinib–rituximab for the treatment of symptomatic Waldenström macroglobulinaemia. The proportion of patients without *MYD88* mutations was 20 (15%) of 133 and the proportion of patients who had a major response was 54%.[10] Both of these proportions were higher than previously reported with ibrutinib alone (8% without *MYD88* mutations *vs* 0% with major response).[44] Explanations for these results might include the use of different detection techniques and differences in bone marrow burden of disease, both of which could have affected the sensitivity of the mutational analyses.[45,46] Updated data presented at the 2018 American Society of Hematology (ASH) Annual Meeting showed a 36-month progression-free survival of 64% (95% CI not provided) for patients with *CXCR4* mutations and 84% (95% CI not provided) for patients without *CXCR4* mutations, suggesting an adverse effect of *CXCR4* mutations for patients with Waldenström macroglobulinaemia who are treated with ibrutinib and rituximab.[47] However, the time to response appeared similar for patients with Waldenström macroglobulinaemia with *CXCR4* mutations (3 months [95% CI not provided]) and without *CXCR4* mutations (2 months [95% CI not provided]) treated with ibrutinib and rituximab. Given the absence of an ibrutinib with placebo group in the INNOVATE study, there is an ongoing debate on the choice between ibrutinib monotherapy versus ibrutinib plus rituximab.

Ibrutinib has been shown to penetrate the CNS and isolated case reports have suggested ibrutinib is effective in the treatment of patients with Waldenström macroglobulinaemia with Bing-Neel syndrome.[48–59] A multicentre retrospective study evaluated ibrutinib in 28 patients with pathologically confirmed Bing-Neel syndrome.[53] Half of the patients in this study had 560 mg ibrutinib, and the other half had 420 mg; both were taken orally once daily. Symptomatic improvements were seen in 21 (81%) of 26 patients and radiological improvements were seen in 9 (60%) of 15 patients within 3 months of ibrutinib initiation. Half of the patients cleared the disease from the cerebrospinal fluid. 2-year event-free survival was 80% (95% CI 58–91).

The risk of bleeding, hypertension, and atrial arrhythmia is increased while on ibrutinib. Ibrutinib should be used with caution in patients with ongoing bleeding diathesis or uncontrolled arrhythmia. Perioperative bleeding can be managed by discontinuing ibrutinib a few days before, the day of, and a few days after each surgical procedure. The length of the temporary discontinuation depends on the invasiveness of the procedure. Atrial fibrillation should be initially managed with β blockers, anticoagulation, or anti-arrhythmic drugs. Cardioversion and cardiac ablation can be considered in patients with persistent symptoms. The calcium channel blockers diltiazem and verapamil interact with ibrutinib and should be avoided. Other relevant adverse events include ibrutinib withdrawal symptoms and IgM rebound upon ibrutinib discontinuation. Withdrawal symptoms characterised by fatigue, fever, or night sweats might occur in 20% of patients with Waldenström macroglobulinaemia who are temporarily holding ibrutinib, which can be managed with oral prednisone (10 mg) twice daily during the hold.[54] Ibrutinib withdrawal symptoms improve rapidly after reinitiating ibrutinib therapy. An increase in serum IgM concentration can also occur while temporarily holding ibrutinib, which should not be considered treatment failure, as serum IgM concentrations decrease upon restarting ibrutinib. In patients who stop taking ibrutinib because of disease progression or unacceptable toxicity, 50% of patients have an IgM rebound within the first 4 weeks of discontinuing therapy.[55] The subsequent treatment following progression on ibrutinib should be started promptly after ibrutinib discontinuation, and consideration should be given to bridging therapy with ibrutinib in combination with the next line of treatment for one or two cycles before completely stopping ibrutinib. Plasmapheresis is recommended if symptomatic hyperviscosity develops.

A phase 2 study evaluated acalabrutinib in 106 patients with Waldenström macroglobulinaemia, of whom 14 were treatment naive and 92 were previously treated.[39] At a median follow-up of 27 months (IQR 26–30), acalabrutinib was associated with an overall response rate of 93% in previously untreated and in treatment-naive patients. The partial response rate in 14 patients without *MYD88* mutations was 64%. Major response rates were 80% in previously untreated patients and 79% in treatment-naive patients. VGPR rates were 9% in previously untreated patients and 0% in treatment-naive patients, and 24-month progression-free survival was 82% (95% CI 72–89) in relapsed or refractory patients and 90% (95% CI 47–99)in treatment-naive patients. *MYD88* and *CXCR4* mutations were not evaluated in most participants in this clinical trial. Most common grade 3 (or worse) adverse events included neutropenia and lower respiratory tract infections. The proportion of patients who had atrial fibrillation was 5%. Common adverse events with acalabrutinib include headache, diarrhoea, bruising, fatigue, nausea, and arthralgia.

Maintenance rituximab

Maintenance rituximab was retrospectively evaluated in patients with Waldenström macroglobulinaemia who received induction rituximab-containing regimens and was reported to be associated with improved progression-free survival and overall survival in patients receiving maintenance versus observation.[24,56,57] Results of the randomised MAINTAIN study (NCT00877214)[22] were presented at the 2019 ASH Annual Meeting, in which 218 patients with Waldenström macroglobulinaemia who attained at least a partial response to bendamustine plus rituximab induction were randomly assigned to 2 years of maintenance rituximab (given every 2 months) versus observation.The median progression-free survival in the maintenance group was 101 months (95% CI not provided) and the median progression-free survival in the observation group was 83 months (95% CI not provided). However, this difference was not statistically significant. The median overall survival was not reached in either the maintenance or observation group. Maintenance rituximab should not be recommended for patients with Waldenström macroglobulinaemia who attained partial response or better after chemoimmunotherapy.

Haematopoietic stem-cell transplantation

The use of autologous and allogeneic haematopoietic stem-cell transplantation (HSCT) in patients with Waldenström macroglobulinaemia is limited to small case series and registry studies without comparator groups. The European Society for Blood and Marrow Transplantation (EBMT) reported on 158 patients with Waldenström macroglobulinaemia who had autologous HSCT.[58] Progression-free survival at 5 years was 40% (95% CI 31–50) and overall survival at 5 years was 69% (95% CI 60–77). The non-relapse mortality at 1 year was 4% (95% CI 2–8) with a cumulative incidence of secondary malignancies at 8% (95% CI 4–16) at 5 years. The EBMT also reported on their experience with allogeneic HSCT in 86 patients with Waldenström macroglobulinaemia, 37 of whom underwent myeloablative conditioning, and 49 of whom underwent reduced intensity conditioning (RIC).[59] Progression-free survival at 5 years was 56% (95% CI 40–72) and overall survival at 5 years was 62% (95% CI 46–78) for myeloablative conditioning. For RIC, progression-free survival at 5 years was 49% (95% CI 34–63) and overall survival at 5 years was 64% (95% CI 48–79). The non-relapse mortality at 3 years was 33% (95% 20–52) for myeloablative conditioning and 23% (95% CI 13–38) for RIC. A consensus document on HSCT for Waldenström macroglobulinaemia treatment was presented at the 2017 ASH Annual Meeting.[60] Consensus was reached, among other items, that autologous HSCT is not appropriate for first-line therapy in patients who are responding to induction therapy, autologous HSCT is appropriate following second or subsequent relapses in high-risk patients (ie, aggressive clinical behaviour or refractory to previous therapies) with chemosensitive disease, and HSCT should not be considered in patients who are BTK inhibitor-naive, provided that BTK inhibitors are available.

Treatment recommendations

There was consensus that chemoimmunotherapy (CDR, or bendamustine plus rituximab), BDR, ibrutinib alone, and ibrutinib plus rituximab are preferred options for primary therapy in patients with symptomatic Waldenström macroglobulinaemia. These regimens can also be used in the management of relapsed or refractory patients. However, there was no consensus on which treatment regimen provides the best safety and efficacy profile. Central to this lack of consensus is the absence of prospective randomised studies comparing these regimens. Specifically, there was no consensus on the recommendations for fixed duration regimens (CDR, bendamustine plus rituximab, or BDR) or indefinite duration regimens (ibrutinib or ibrutinib plus rituximab). However, there was consensus that there are currently no convincing data to recommend the combination of ibrutinib and rituximab over ibrutinib alone. The INNOVATE study compared ibrutinib and rituximab with placebo and rituximab, and no ibrutinib monotherapy group was included, therefore no conclusions could be made in this regard. The choice of primary and subsequent therapy should be personalised, considering the toxicity profile, administration schedule and route, drug accessibility, and patient's preference (panel). For patients with Bing-Neel syndrome, treatment options that effectively cross the blood–brain barrier should be used and include ibrutinib, fludarabine, bendamustine, methotrexate, and cytarabine.

Specific for the use of ibrutinib, there was consensus on recommending *MYD88* and *L265P* mutation testing before treatment selection. There was consensus on recommending the use of PCR-based assays for detection of *MYD88* mutations. Most consensus panel members recommended against the use of ibrutinib alone in patients without *MYD88* mutations. In these patients, ibrutinib and rituximab can be considered. However, there is a high degree of variability in the sensitivity of different available tests, along with the difficulties with cell selection before *MYD88* testing, and a small proportion of patients with Waldenström macroglobulinaemia who have non-Leu265Pro *MYD88* mutations, so a negative PCR test should be interpreted with great caution and followed by gene sequencing before making treatment decisions from that test. There was no consensus on the recommendation of routinely doing *CXCR4* mutational testing in the community setting, partly because of the technical difficulties of reliably detecting the numerous *CXCR4* mutations in clinical practice. However, there was consensus on the use of *CXCR4* mutational testing in academic settings for further study, and refining and standardising *CXCR4* mutation detection methods.

Panel: **Treatment algorithm for patients with symptomatic Waldenström macroglobulinaemia***

Preferred treatment options

- Bendamustine plus rituximab
- Bortezomib, dexamethasone, and rituximab
- Cyclophosphamide, dexamethasone, and rituximab
- Ibrutinib (with or without rituximab)

Treatment recommendations

- Avoid bortezomib and vincristine in patients with neuropathy
- Avoid carfilzomib in patients with cardiac disease or patients who are older than 65 years
- Avoid nucleoside analogues in patients who are candidates for stem-cell transplantation
- Consider delaying rituximab if serum IgM concentrations are greater than 4000 mg/dL
- Consider ofatumumab in patients who are intolerant to rituximab

Other treatment options

- Acalabrutinib
- Carfilzomib, dexamethasone, and rituximab
- Fludarabine and rituximab
- Ixazomib, dexamethasone, and rituximab
- R-CHOP
- R-CVP
- Rituximab
- Ofatumumab

R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CVP=rituximab, cyclophosphamide, vincristine, and prednisone. *Treatment choice might be determined by the clinical, laboratory, and genomic features of the patients; drug availability and coverage based on respective national and institutional guidelines should be considered.

See Online for appendix

The use of novel proteasome inhibitors (ie, carfilzomib and ixazomib) is limited by accessibility outside of the USA. Within the USA, carfilzomib and ixazomib, both in combination with rituximab and dexamethasone, are commercially available and endorsed by the National Comprehensive Cancer Network. Despite their efficacy, nucleoside analogues (ie, fludarabine and cladribine) should be reserved for patients with late relapses given their specific toxicity profile and increased risk of myeloid neoplasms in exposed patients. In patients who are refractory to rituximab, alkylating single drugs, proteasome inhibitors, and BTK inhibitors can be used. With the advent of effective and well tolerated novel drugs, the role of HSCT in patients with Waldenström macroglobulinaemia should be limited to patients with relapsed disease after exposure to chemoimmunotherapy and BTK inhibitors.

Other recommendations

Given the IgM flare observed in patients treated with rituximab, alone or in combination, rituximab should be withheld during the first one or two cycles of combination therapy in patients with Waldenström macroglobulinaemia who have serum IgM concentrations greater than 4000 mg/dL to minimise the risk of an IgM flare, as supported by the National Comprehensive Cancer Network.[61] At any time, urgent plasmapheresis should be used to promptly treat patients with suspected symptomatic hyperviscosity (eg, nosebleeds, headaches, retinal changes), cryoglobulinaemia (eg, livedo reticularis, painful ulcers in lower extremities), or cold agglutinin disease (eg, acute haemolysis). All patients with Waldenström macroglobulinaemia receiving proteasome inhibitor-based therapy should receive prophylactic therapy against herpes zoster. *Pneumocystis jirovecii* and herpes zoster prophylaxis should be considered in patients treated with fludarabine or bendamustine-containing regimens. Hypogammaglobulinaemia can be seen in 60% of patients with Waldenström macroglobulinaemia who are treatment naive and, in most cases, serum IgG and IgA concentrations do not improve with response to therapy.[62] Intravenous immunoglobulin therapy should be considered in patients with Waldenström macroglobulinaemia and symptomatic hypogammaglobulinaemia, which could be defined as recurrent bacterial respiratory infections in patients with low serum IgG concentrations. All patients should receive yearly vaccinations for seasonal influenza and consider vaccines against *Pneumococcus pneumoniae* and herpes zoster (recombinant vaccine). In patients who are eligible for autologous HSCT, stem cells should be collected before nucleoside analogue exposure.

Recent clinical trials

The consensus panel endorses enrolment of patients with symptomatic Waldenström macroglobulinaemia in ongoing clinical trials (appendix p 2).

Proteasome inhibitors

Subcutaneous bortezomib is being evaluated in two randomised studies. A phase 2 randomised study is evaluating subcutaneous bortezomib, cyclophosphamide, and rituximab versus oral fludarabine, cyclophosphamide, and rituximab in previously untreated patients with Waldenström macroglobulinaemia (NCT01592981). Primary outcome is disease response at 6 months of therapy. Secondary outcomes are toxicity, progression-free survival, overall survival, and quality of life. A phase 3 study is evaluating CDR with and without subcutaneous bortezomib and completed accrual of 202 participants by November, 2018 (NCT01788020). The primary outcome is progression-free survival and secondary outcomes are response rate, time to treatment failure, and overall survival.

Ixazomib, dexamethasone, and rituximab (IDR) was also evaluated in a phase 2 study in 60 previously treated patients with Waldenström macroglobulinaemia.[32] IDR therapy was composed of eight cycles of induction followed by 2 years of quarterly maintenance rituximab subcutaneous injections, if patients attained a partial

response to induction therapy. Overall response rate was 88%, major response rate was 68%, and the rate of VGPR or better was 24%. The median progression-free survival was not yet reached at 20 months of follow-up. Grade 3 adverse events were reported in 28% of patients and grade 4 adverse events were reported in 10% of patients. Six patients died during the trial, including two deaths due to disease progression and one death from progressive multifocal leucoencephalopathy.

BTK inhibitors

A phase 1/2 study evaluated zanubrutinib in 77 patients with Waldenström macroglobulinaemia, including 24 patients who were treatment naive and 53 who were previously treated.[63] At a median follow-up of 24 months, zanubrutinib was associated with an overall response rate of 92%, major response rate of 82%, VGPR rate of 41%, and 24-month progression-free survival of 81% (95% CI 68–89). Most genotyped patients with *MYD88* mutations in this study did not have identified *CXCR4* mutations, which could have contributed to the high VGPR reported in this study. Adverse events of minor bruising or bleeding and atrial fibrillation (5%) were observed with zanubrutinib. A randomised phase 3 study evaluating zanubrutinib versus ibrutinib in symptomatic patients with Waldenström macroglobulinaemia has completed accrual and 210 patients have been enrolled (NCT03053440). The study design has three groups: oral zanubrutinib 160 mg twice daily (cohort A), oral ibrutinib 420 mg once daily (cohort B), and oral zanubrutinib 160 mg twice daily in patients with Waldenström macroglobulinaemia without *MYD88* Leu265Pro mutations (cohort C). Results from cohorts A and B were published in July, 2020.[64] 102 patients were randomly assigned to the zanubrutinib group and 99 patients to the ibrutinib group. VGPR was attained in 29 (28%) of 102 patients on zanubrutinib and in 19 of 99 (19%) patients on ibrutinib. This difference was not statistically significant. Zanubrutinib was associated with a lower rate of atrial fibrillation (2%) than ibrutinib (15%), but there was a higher rate of neutropenia with zanubrutinib (29%) than with ibrutinib (13%). Preliminary results from cohort C showed that zanubrutinib induced responses in patients without *MYD88* mutations, with an overall response rate of 77%, major response of rate 54%, and VGPR rate of 15%.[65]

Data on the novel BTK inhibitor tirabrutinib were presented at the 2019 ASH Annual Meeting.[66] Tirabrutinib was evaluated at a dose of 480 mg by mouth once daily until disease progression of unacceptable toxicity in 27 patients with Waldenström macroglobulinaemia (18 treatment naive and nine previously treated). Responses were assessed by an independent review committee. The overall response rate was 94% and the major response rate was 78% in treatment-naive patients, whereas the overall response rate was 100% and major response rate 89% in previously treated patients. Rash was a common adverse event reported in 41% of patients. Grade 3 neutropenia was reported in 7% of patients.

The acquisition of *BTK* mutations have been associated with resistance to BTK inhibitors in patients with Waldenström macroglobulinaemia, partly because of reactivation of MAPK3 and MAPK1.[67] Predictably, *BTK* mutations can render current covalent BTK inhibitors (ie, ibrutinib, acalabrutinib, zanubrutinib, tirabrutinib) ineffective. Second generation, non-covalent BTK inhibitors (eg, vecabrutinib, LOXO-305) are being investigated in patients with Waldenström macroglobulinaemia who had disease progression on ibrutinib. Preclinical studies have suggested that modulation of the kinase HCK can overcome the resistance to BTK inhibitors associated with *BTK* or *PLCG2* mutations.[68] Dasatinib has shown to be a potent HCK inhibitor, and a pilot study in patients with Waldenström macroglobulinaemia and *BTK* or *PLCG2* mutations with disease progression on ibrutinib is ongoing (NCT04115059).

BCL2 antagonists

A multicentre phase 2 clinical trial evaluating venetoclax in patients with Waldenström macroglobulinaemia has completed accrual of participants.[69] 30 patients were enrolled, of whom 15 were previously exposed to BTK inhibitors. Venetoclax dose was escalated weekly to a maximum dose of 800 mg by mouth once daily, which was then continued for a maximum of 2 years. Tumour lysis syndrome monitoring tests were obtained at the time of first exposure and at each dose escalation. With a follow-up of 18 months, preliminary results showed overall response, major response, and overall response was 90%, major response was 83%, and VGPR was 20%, and 18-month progression-free survival was 82% (95% CI not available). Grade 3 (or worse) adverse events included neutropenia (50%), anaemia (8%), and diarrhoea (8%). One laboratory tumour lysis syndrome event and no clinical tumour lysis syndrome events were reported. A study combining ibrutinib and venetoclax in previously untreated patients with Waldenström macroglobulinaemia is ongoing (NCT04273139).

PI3K inhibitors

A phase 1/2 study evaluated idelalisib in ten patients with previously treated Waldenström macroglobulinaemia.[70] Idelalisib at 150 mg by mouth twice daily was associated with an 80% overall response rate. Toxicity was not specifically reported in patients with Waldenström macroglobulinaemia. Long-term follow-up showed median progression-free survival of 22 months (95% CI 1–66).[71] Most common grade 3 (or worse) adverse events included neutropenia (28%), diarrhoea (28%), and increased liver enzymes (16%). A phase 2 study that aimed at evaluating idelalisib at a dose of 150 mg by mouth twice daily in 30 patients with previously treated Waldenström macroglobulinaemia was terminated early due to grade 3 (or worse) increased

Search strategy and selection criteria

To formulate recommendations based on evidence, a literature search was done of PubMed with the keyword "Waldenström" between Jan 1, 2010, and Feb 29, 2020, with no language restrictions. Abstract presentations from the annual meetings of the American Society of Hematology, the European Hematology Association, the American Society of Clinical Oncology, the European Society of Medical Oncology, the International Conference in Malignant Lymphoma, and the International Workshop for Waldenström macroglobulinaemia, between Jan 1, 2017, and Dec 31, 2019, were identified following a similar strategy using "Waldenström" as a keyword. Prospective phase 2 and 3 studies and retrospective studies involving 50 or more patients were included. Studies not reporting on clinical trials or clinical observations were excluded in the first round of study selection. Duplicate studies, studies not relevant to current clinical care, and retrospective studies involving fewer than 50 patients were excluded in the second round of study selection. Our search rendered 2468 articles for initial review, of which 2316 articles were excluded because they did not report on clinical trials (appendix p 1). From the remaining 152 articles, 115 were excluded upon further review, with 37 studies finally included in the present document.

liver enzyme concentrations in three of the first five enrolled patients.[72]

The combination of idelalisib and obinutuzumab was evaluated in 50 previously treated patients with Waldenström macroglobulinaemia.[73] Overall response rate was 90% and major response rate was 76%. With a median follow-up of 18 months, the median progression-free survival was 25 months (95% CI not provided). Elevated liver enzyme concentrations were observed in 25% of patients, and 50% stopped the combination prematurely because of drug toxicity.

Enrolment of patients with Waldenström macroglobulinaemia in a study evaluating the PD-1 monoclonal antibody tislelizumab in combination with zanubrutinib was halted after rapid onset, life-threatening autoimmune haemolysis in both of the patients enrolled,[74] suggesting caution in the use of drugs that target PD-1 for patients with Waldenström macroglobulinaemia.

Priorities in future clinical trials

Treatment options for patients with Waldenström macroglobulinaemia are increasing and more targeted therapies are being used in everyday practice and clinical trials. However, the use of currently available targeted therapies needs further optimisation. Waldenström macroglobulinaemia is a rare disease; therefore, it is important to prioritise studies that will drive the development of innovative, effective, and safer therapies. Large studies require international collaboration and partnerships between academia, industry, regulatory authorities, and the global patient community. Ancillary translational and biological studies should be part of every clinical trial of Waldenström macroglobulinaemia treatments.[75] Small studies that are focused on disease biology can enable clinical implementation of new therapies. The goal of future studies should be the development of personalised treatment approaches. Another important aspect for clinical trials in Waldenström macroglobulinaemia treatment is the determination of clinically relevant endpoints. Overall survival and progression-free survival might not be feasible primary endpoints, and validated surrogate endpoints should be developed to allow timely evaluation of new treatments. Although complete response rates are low with current therapies, new options could increase the proportion of patients who have this outcome. When complete response rates have improved, minimal residual disease-based approaches could be developed to guide treatment duration. Treatment goals for patients depending on age, performance status, comorbidites, and genomic profiles could be different, and studies should incorporate the priorities of the patient community (ie, patient reported outcomes).

With the increasing use of BTK inhibitors in treatment of Waldenström macroglobulinaemia, the duration of therapy and the comparison of fixed duration versus continuous therapy becomes relevant. Anti-CD20 antibodies plus chemotherapy regimens are widely used in all settings providing a fixed duration therapy, but have not been compared with indefinite duration regimens. The ongoing RAINBOW study is currently comparing CDR versus ibrutinib plus rituximab (NCT04061512). The panel decided that key studies should be prioritised in newly diagnosed patients and should include the exploration of fixed duration chemotherapy-free regimens, such as combinations of anti-CD20 monoclonal antibodies with BCL2 inhibitors,[76] BTK and BCL2 inhibitors,[77] and proteasome and BTK inhibitors. Another important clinical question remains the evaluation of combination versus sequential approaches in the context of efficacy to toxicity and financial cost. For patients with relapsed or refractory disease, duration of therapy also remains important, but chemotherapy-free combinations with non-cross resistance to BTK inhibitors, should be evaluated. Cellular-based therapies are undergoing evaluation in B-cell malignancies and multiple myeloma, and their optimal use in Waldenström macroglobulinaemia treatment should be carefully evaluated in the context of the available targeted therapies. Cost-effectiveness, toxicity, and quality of life are major concerns and the sustainability of the health-care system with the increasing use of expensive therapies should remain a focus when designing future clinical trials.

Contributors

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