review articles

Waldenstrom Macroglobulinemia: Tailoring Therapy for the Individual

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abstract

With the introduction of multiple new effective therapeutic options for the treatment of macroglobulinemia, a structured approach to management of this rare lymphoma is currently needed. A review of phase II and III treatment trials over the past 20 years was performed, and high-quality trials are summarized in this manuscript. Because of the lack of large prospective trials comparing different classes of therapy, a uniform recommendation applicable to all patients cannot be made, and the approach must be individualized incorporating patient preferences, comorbidities, and the range of therapeutic toxicities. Therapeutic options for patients with newly diagnosed and previously treated macroglobulinemia are presented on the basis of the best available evidence in the literature.

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INTRODUCTION

Waldenstrom macroglobulinemia is defined as a lymphoplasmacytic lymphoma associated with an immunoglobulin M (IgM) monoclonal protein of any size.[1] The majority of patients present with progressive anemia associated with modest lymphadenopathy, occasionally with symptoms associated with hyperviscosity as a consequence of the properties of a large IgM monoclonal protein.[2] This lymphoma is incurable and as a consequence, therapy is reserved for symptomatic patients.[3] There is no threshold of IgM above which therapy is required,[4] and many such patients with so-called smoldering macroglobulinemia may be observed for years before they develop anemia or hyperviscosity syndrome. Asymptomatic patients require regular monitoring for changes that would require therapeutic intervention. An online risk tool exists that estimates median time to progression on the basis of percentage bone marrow infiltration, IgM protein level, beta 2 microglobulin level, and serum albumin. This tool is found at Web page application.[5] Clonal hematopoiesis is present in 14% of patients with macroglobulinemia[6] and, when present in smoldering macroglobulinemia, increases the risk of progression to symptomatic disease.[6]

Patients with an IgM monoclonal protein fall into one of four categories: (1) IgM monoclonal gammopathy of undetermined significance (MGUS)—completely asymptomatic usually incidental; (2) smoldering macroglobulinemia—fulfills criteria for macroglobulinemia but asymptomatic; (3) IgM-related disorder—this includes IgM amyloidosis, cold agglutinin disease, type 2 cryoglobulinemia, and IgM-mediated MGUS neuropathy, associated with high titer myelin-associated glycoprotein antibodies; and (4) symptomatic macroglobulinemia. Consensus-defined indications for the initiation of therapy include hemoglobin under 10 g/dL, platelet count under 100,000/μL because of bone marrow infiltration with lymphoplasmacytic lymphoma, symptomatic hyperviscosity most usually manifest as oronasal bleeding or retinal hemorrhage, and rarely central vein occlusion.[7] An IgM-related disorder, when symptomatic, qualifies for therapy intervention.[8] The international prognostic scoring system (staging) is given in Table 1; of interest is the absence of LDH in predicting outcomes.[9]

BIOLOGY AND CLINICAL COURSE

Macroglobulinemia represents 1%-2% of non-Hodgkin lymphoma, with an incidence of about three per million per year and its incidence is increasing.[10] Age of onset is a median of 70 years at diagnosis. Reported median survival exceeding 10 years is now common.[11] Comorbidities in this aged population and the risks associated with therapy-related complications that will affect the patient's quality of life in the long term become important considerations in choosing therapy. In patients older than 75 years at diagnosis, only 33% (at 15 years) will die of causes directly related to the macroglobulinemia and 49% will die of unrelated causes. Between age 65 and 74 years, the risk of death from macroglobulinemia is 29.2% compared with 34.2% from unrelated causes. Only in patients younger than 65 years at diagnosis does the 15-year mortality from Waldenstrom macroglobulinemia (23.2%) exceed the risk of death from other causes (14.7%).[12]

The defining mutation of macroglobulinemia is MYD88^{L256P}. It is useful to know the mutational status

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CONTEXT

Key Objective

With the rapid introduction of new therapies for macroglobulinemia, it is important to know when therapy is required and what considerations are required to individualize therapy for a given patient.

Knowledge Generated

Therapeutic algorithms have been generated for rapid assessment.

Relevance

This paper will allow rapid decision making when seeing a new patient with macroglobulinemia.

because it is found in 95% of patients with macroglobulinemia and is confirmatory for the diagnosis. The presence of this mutation, however, does not determine the need for therapy since it is found in more than 60% of patients with IgM MGUS.[13] Other B-cell neoplasms can manifest mutations in MYD 88. It has been reported in 10 of 60 patients with chronic lymphatic leukemia, 3 of 13 with hairy cell leukemia, 1 of 11 mantle cell lymphoma, and one of five marginal zone lymphoma.[14] Patients with MYD88-negative macroglobulinemia are older, have a lower degree of bone marrow infiltration, and have a lower score on the International Prognostic Index.[15] Mutations in $MYD88^{L256P}$ have therapeutic implications in that patients with wild-type MYD88 appear to have a lower response rate to BTK-based therapies but not with therapy on the basis of bendamustine, a proteasome inhibitor, or cyclophosphamide.[16,17] CXCR4-mutated patients are more likely to develop symptomatic hyperviscosity, lower frequency of lymphadenopathy, and lower beta 2 microglobulin.[18] Mutations in CXCR4 are also important therapeutically and found in more than 30% of patients with macroglobulinemia. Its presence is associated with clinical resistance to ibrutinib and varying levels of resistance to bendamustine and bortezomib.[17,19]

TREATMENT

Before any discussion of therapy, the goals of treatment need to be established. One must keep in mind the original indication for intervention. Questions to be asked during therapy include what has happened to the level of hemoglobin or have symptoms of hyperviscosity resolved? If adenopathy was present, has this resolved. The criteria of response are all on the basis of the percentage reduction of the IgM monoclonal protein.[20] Unlike multiple myeloma, where deeper responses are proven to translate to improved progression-free survival (PFS) and overall survival (OS), the same cannot be said for macroglobulinemia. Although PFS and time to next therapy predict OS in macroglobulinemia, response depth beyond a partial response (PR)[21,22] has not consistently been demonstrated to result in better outcome.[23] In other words, a patient initiating therapy with an IgM level of 6,000 mg/dL that plateaus with an IgM of 2,800 should not be considered a therapeutic failure if the end points for initiating therapy have improved.

TABLE 1. International Prognostic Scoring System for Waldenstrom's Macroglobulinemia

Factor	Cutoff
Age, years	> 65
Hemoglobin, g/dL	≤ 11.5
Platelet count	≤ 100 × 10^9/L
β2-microglobulin, mg/L	> 3
Serum monoclonal IgM, g/dL	> 7.0
Risk category	**Score**
Low risk	0 or 1 factor (≤ 65 years)
Intermediate risk	2 factors OR age > 65 years
High risk	> 2 factors

Abbreviation: IgM, immunoglobulin M.

HYPERVISCOSITY

Management of hyperviscosity has been recently reviewed.[24] Hyperviscosity syndrome should always be confirmed by the measurement of serum hyperviscosity. Patients who are asymptomatic do not need preemptive plasma exchange even when the serum viscosity levels are elevated. Serum viscosity at diagnosis but not the IgM level is an independent predictor of the time to development of symptomatic hyperviscosity. Hyperviscosity has no impact on survival.[25] Only 15% of patients with an IgM level > 6,000 ultimately develop hyperviscosity syndrome.[25] In the International Waldenstrom Staging System, an IgM level > 7 g is prognostic. However, it is unclear whether this impact reflects a very high tumor mass or reflecting a higher prevalence of hyperviscosity. The presence of retinal hemorrhage is a medical emergency, and plasma exchange should be initiated even when rapidly acting cytoreductive therapy is planned.[2] A single plasma exchange can reduce the viscosity level by 50% even when the IgM level is reduced by only 20% and is often sufficient if immediate chemotherapy is planned.[26]

MONOCLONAL ANTIBODIES

The modern era of therapy for macroglobulinemia began with the introduction of rituximab. CD 20 is uniformly

expressed on the cell surface of lymphoplasmacytic lymphoma. In the originally reported trials, the response rates were 52.6%[27] and 48.3%.[28] These results are inferior to all reported combinations that include rituximab. For most patients with macroglobulinemia, single-agent rituximab should be considered inadequate therapy. Rituximab as a single agent can also produce flare of the IgM level that can result in symptomatic hyperviscosity. Used as a single agent in the presence of extremely high IgM level, the availability of immediate plasma exchange for symptoms or alternatively delaying rituximab until the second or third cycle of multi-agent chemotherapy should be considered.[29,30] Ofatumumab does not appear to offer any therapeutic advantages over rituximab. The response rate reported was 51%, and flare was seen.[31]

ALKYLATING AGENTS

The combination of rituximab cyclophosphamide and dexamethasone was introduced in 2007 and produced an overall response rate of 83%; ≥ PR in 74%.[32] In a study of 72 patients, the median PFS was 35 months.[33] Among 50 relapsed patients with macroglobulinemia treated with this regimen, the response rate was 87% (PFS 32 months). In 50 treatment-naive patients, the response rate was 96% with a median PFS of 34 months. Response rates were not lower in MYD 88 wild-type.[34] Toxicity was primarily myelosuppression and gastrointestinal distress rarely requiring the cessation of therapy. Cyclophosphamide also has the advantage in areas where there are resource constraints. Unfortunately, there is a significant risk of late therapy–related myeloid neoplasm associated with cyclophosphamide, and the prolonged survivals in patients with macroglobulinemia results in a significant actuarial risk of myelodysplastic syndrome. Myelodysplastic syndrome/acute myeloid leukemia deaths were notably increased (N = 46; standardized mortality ratio 4.4, 95% CI, 3.2 to 5.9) among 7,289 lymphoplasmacytic lymphoma patients.[12]

PROTEASOME INHIBITION

Bortezomib, rituximab, and dexamethasone was found to be highly effective in the treatment of macroglobulinemia (Table 2). Unlike alkylating agents, the responses were very fast at a median of 1.4 months. The PR rate was 83%, and the overall response rate was 96%.[35] However, 13 of 16 patients developed peripheral neuropathy, a major consideration for patients destined to live a decade. Neurotoxicity was reduced by administering bortezomib on a weekly basis without significant compromise of response rate. All treatment-naive patients responded, and the objective response rate was 88%[36]; for previously treated patients, the overall response rate was 81% and the objective response rate was 51%. Grade 3 or greater neuropathy was seen in 5%.[37] Bortezomib was added to cyclophosphamide, rituximab, and dexamethasone as part of a phase III trial compared with RCD alone, and the 24-month PFS was 80.6% and 72.8%, respectively (P = not significant).[38] The major response rate was 79.1% and 68.9%, P = not significant. Response was unaffected by mutational status. Peripheral sensory neuropathy was seen in 18% of patients in the bortezomib arm compared with 3% in the cyclophosphamide arm. The addition of bortezomib to alkylating agent–based therapy appears not to provide significant benefit.

Carfilzomib is active in the treatment of macroglobulinemia without producing neuropathy. In a cohort of 27 patients previously unexposed to rituximab or bortezomib, the overall response rate was 87.1%, and 20 of 27 were progression-free at a median follow-up of 15 months.[39]

Ixazomib as a non-neurotoxic orally administered proteasome inhibitor offers obvious advantages in an elderly population. Ixazomib 4 mg weekly with rituximab and dexamethasone resulted in an overall response rate of 96% and an objective response rate of 77%. Median PFS had not been reached at a median follow-up of 22 months.[40] In treatment-naive patients, the same combination resulted in an overall response rate of 96%, an objective response rate of 77%, and a median PFS of 40 months.[41]

A multicenter phase I, II trial with ixazomib, subcutaneous rituximab, and dexamethasone was conducted by the European Collaborative Group. Fifty-nine patients were enrolled with a median age of 69 years. All were previously treated; the overall response rate was 71%, with 14% very good PR. The median duration of response was 36 months. Median time to response was 4 months. After 24 months, PFS and OS were 56% and 88%, respectively. Quality of life was assessed and improved. The advantage of an all-oral regimen combined with subcutaneous rituximab in

TABLE 2. Selected Outcomes With Proteasome Inhibitor–Based Therapy

Regimen	ND/RR	≥ 25%↓IgM; %	≥ 50%↓IgM; %	≥ 90%↓IgM; %	PFS (time)	Reference
BRd	23/0	13	48	35	TTP > 30 months	33
BR	26/0	23	58	8	79% at 1 year	34
BR	0/37	30	46	5	15.6 months	35
CaRd	28/3	19	32	35	75% at 1 year	36
IRd	26/0	19	62	15	75% at 22 months	37

Abbreviations: BR, bortezomib and rituximab; BRd, bortezomib, rituximab, and dexamethasone; CaRd, carfilzomib, rituximab, and dexamethasone; IgM, immunoglobulin M; IRd, ixazomib, rituximab, and dexamethasone; ND, newly diagnosed; PFS, progression-free survival; RR, relapsed refractory; TTP, time to progression.

TABLE 3. Bendamustine-Based Therapies

Regimen	ND/RR	≥ 25%↓IgM; %	≥ 50%↓IgM; %	≥ 90%↓IgM; %	PFS (time)	Reference
B ± R	0/30	3	67	17	13.2 months	39
BR	0/71	5.6	52.1	22.5	60% at 2 years	40
BR	69/0	1	40	56	87% at 2 years	41
BR	22/0				69.5 months	42
BR	288/0	2.5	89.9		78 months	44

Abbreviations: BR, bendamustine and rituximab; IgM, immunoglobulin M; ND, newly diagnosed; PFS, progression-free survival; RR, relapsed refractory.

previously treated patients is deserving of consideration as second-line therapy. No direct comparisons exist with ixazomib, bendamustine, or a Bruton tyrosine kinase inhibitor.[41] Currently, I do not use proteasome inhibitors as first-line therapy, primarily because of their toxicity profile. I generally reserve their use for patients who are not responsive to either bendamustine or a BTK inhibitor.

BENDAMUSTINE

In a phase II trial, bendamustine with and without rituximab resulted in an overall response rate of 83.3% and a PFS of 13.2 months in relapsed refractory disease (Table 3).[42] A second trial in 71 relapsed refractory patients reported an overall response rate of 80.2%, and the major response rate was 74.6%. PFS was over 19 months. No patients developed therapy-related myeloid neoplasm. The major toxicity was myelosuppression.[43] Among 69 newly diagnosed patients, the overall response rate was 97%, the objective response rate was 96%, and the 2-year PFS was 87%. Grade 3 and 4 nonhematologic adverse events were predominantly infectious in 9. There were no therapy-related deaths.[44]

A large phase III trial of rituximab cyclophosphamide doxorubicin vincristine prednisone (R-CHOP) and R-bendamustine in low-grade lymphomas included 41 with macroglobulinemia.[45] Twenty-two received R-bendamustine and 19 received R-CHOP. PFS with bendamustine was 69.5 months compared with 28.1 months with R-CHOP. The response rate in both groups was 95%. The toxicity profile favored R-bendamustine with less gastrointestinal toxicity and fewer infections.[45] When rituximab bendamustine was compared retrospectively with rituximab, cyclophosphamide, and dexamethasone, overall response rate, major response rate, time to next therapy, and event-free survival with R-bendamustine was superior to those with rituximab, cyclophosphamide, and dexamethasone, or bortezomib, rituximab, and dexamethasone.[46]

Two hundred ninety-three patients were uniformly treated with rituximab and bendamustine and were then randomly assigned to 2 years of rituximab maintenance or observation. The median age was 67 years. The median PFS was 78 months and 5-year OS of 78%. There was one acute myelogenous leukemia and one myelodysplastic syndrome for an overall second hematologic malignancy rate of 0.7%. There was no statistically significant difference in PFS between the two arms at a median of 5.9 years.[47] Bendamustine has been combined with bortezomib. In a phase II study, the 18-month PFS in relapsed disease will be > 65%. The overall response rate was 82% with 50% complete and very good PRs.[48]

BRUTON TYROSINE KINASE INHIBITION

Ibrutinib

In a prospective study of ibrutinib in 63 symptomatic previously treated patients, the median time to a minor response was 4 weeks (Table 4). The overall response rate was 90.5%, and the major response rate was 73%. Wild-type MYD88 resulted in a response rate of 71.4%, of which only 28.6% were major responses.[49] Side effects included atrial fibrillation, diarrhea, neutropenia, and thrombocytopenia. Long-term follow-up confirmed an overall and a major response rate of 90.5% and 79.4%, respectively. There were no major responses in patients with wild-type MYD88. A lower response rate with CXCR4 mutation was confirmed.[50] When ibrutinib was used in 30 untreated patients with therapy planned to progression or toxicity, the overall and major response rates, respectively, were 100% and 83%. Response rate was lower in patients who had mutated CXCR4. The 18-month PFS was 92%. Toxicities

TABLE 4. Bruton Tyrosine Kinase Inhibitor-Based Therapy

Regimen	ND/RR	≥ 25%↓IgM; %	≥ 50%↓IgM; %	≥ 90%↓IgM; %	PFS (time)	Reference
Ibrutinib	0/63	11.1	49.2	30.2	54% at 5 years	47
Ibrutinib	30/0	17	63	20	92% at 18 months	48
Ibrutinib-R	34/41	20	47	26	82% at 30 months	50
Acalabrutinib	14/92	14/13	79/72	0/9	90/82 at 2 years	54
Zanubrutinib	19/83	17	49	28	85% at 18 months	55

Abbreviations: IgM, immunoglobulin M; ND, newly diagnosed; PFS, progression-free survival; RR, relapsed refractory.

included arthralgia, bruising, neutropenia, upper respiratory tract infections, atrial fibrillation (10%), and hypertension.[51] In a final report, the 4-year PFS is 76%, with atrial fibrillation occurring in 20% of patients.[52] The lower response rate in patients with CXCR 4 mutation led to a trial of a CXCR4 inhibitor, ulocuplumab. When combined with ibrutinib, the response rate was 100% in the 12 treatment-evaluable patients.[53] A trial of a second inhibitor of CXCR4 is underway with ibrutinib (ClinicalTrials.gov identifier: NCT04274738).

The abrupt withdrawal of ibrutinib because of toxicity or surgery can result in a rapid rise in the IgM level, flare, associated with an exacerbation in symptoms of macroglobulinemia. Ibrutinib should not be stopped unless progression is suspected and if it is discontinued, monitoring within the first week for a rise in the IgM and reductions in hemoglobin are required. Currently, all bruton tyrosine kinase inhibitor (BTKi) are designed for indefinite use and not for a fixed duration. The risk of atrial fibrillation of 10% for ibrutinib is a major disadvantage to its use. The development of atrial fibrillation may require hospitalization for rate control, the possibility of cardioversion or atrial ablation, and long-term anticoagulation using a medication where the major bleeding risk is 3%. Because all BTKi interact with inhibitors of CYP3A4, caution is required if the patient is on multiple other medications. Concurrent use of ibrutinib and grapefruit juice may result in increased ibrutinib exposure. Hypertension is seen in up to 20% of patients.

A phase III trial randomly assigned treatment-naive and previously treated patients to rituximab or rituximab and ibrutinib. Rituximab was the inferior therapy. At 30 months, the PFS rate was 82% with ibrutinib and rituximab versus 28% with rituximab. This benefit was independent of mutational status. The major response rate was 72% and 32%, respectively. Atrial fibrillation was seen in 12% of ibrutinib-treated patients. Hypertension was seen in 13%. Flare was seen in only 8% of the ibrutinib arm compared with 47% in the rituximab arm. This trial failed to address the question of whether ibrutinib rituximab is superior to ibrutinib alone.[54] Single-agent rituximab is an inferior therapy for symptomatic macroglobulinemia. In the reported final analysis, higher response rates (PR or better) were observed with ibrutinib-rituximab (76% *v* 31% with placebo-rituximab; $P < .0001$). Median time to next therapy was not reached with ibrutinib-rituximab versus 18 months with placebo-rituximab regardless of MYD88 or CXCR4 mutation status.[55]

Although there is no single best initial therapy for patients with macroglobulinemia, ibrutinib is essential for those patients who have central nervous system involvement, the so-called Bing-Neel syndrome. Most publications are single case reports and small case series. Nonetheless, sustained clinical improvement and improvement in imaging of the leptomeninges have been reported with ibrutinib.[56] In a case series of 28 patients, ibrutinib at doses of 420 mg and 560 mg resulted in clinical and imaging improvement in 85% and 60% of patients, respectively, at 3 months. Ibrutinib should be considered the first choice of therapy when the central nervous system is involved with lymphoplasmacytic lymphoma.[57]

Acalabrutinib

Acalabrutinib is approved for the treatment of chronic lymphatic leukemia and mantle cell lymphoma. A multicenter phase II trial was performed in untreated and previously treated macroglobulinemia. Acalabrutinib was given until progression or toxicity. One hundred six patients were treated. In both untreated (N = 14) and relapsed patients (N = 86) the response rate was 93% (N = 86). Neutropenia was seen in 16% and pneumonia in 7%, but atrial fibrillation grade 3 for was only seen in 1%. This agent appears to have a better safety profile than ibrutinib. Adverse events leading to discontinuation of therapy occurred in 7% of patients. Response duration and PFS were not statistically different between treatment-naive and relapsed patients.[58] The overall response rate in patients with mutated MYD 88 and in patients with wild-type MYD 88 was, respectively, 94% and 79%. The comparison was 36 and 14 patients, respectively; so, statistics could not be applied.

Zanubrutinib

The phase III Aspen trial randomly assigned patients 1:1 to ibrutinib or zanubrutinib. Two hundred one patients were randomly assigned; the ≥ very good partial response (VGPR) rate was 28% for zanubrutinib and 19% with ibrutinib ($P = .09$). Median duration of response and PFS was not different between the two groups. Muscle spasms and pneumonia leading to discontinuation of therapy were less common with zanubrutinib. Neutropenia was higher with zanubrutinib, but grade 3 infection or greater was similar in both arms. Both agents were highly effective in the treatment of macroglobulinemia. Zanubrutinib was associated with less atrial fibrillation.[59] Grade 3 or greater atrial fibrillation was seen in 7.1% of the ibrutinib group and 0% of the zanubrutinib group. All-grade diarrhea was seen in 32.7% of ibrutinib-treated patients and 21.8% of zanubrutinib patients. In a MYD88 substudy of patients with wild-type MYD88, 27% achieved VGPR and 50% a PR or better. The PFS and OS rates at 18 months were 68% and 88%, respectively. Zanubrutinib monotherapy can induce high-quality responses in wild-type MYD88.[60]

Venetoclax

In vitro studies of macroglobulinemia cells demonstrates high levels of expression of BCL2, which upregulates after exposure to ibrutinib, suggesting enhanced sensitivity to venetoclax after failure of a BTK inhibitor.[61] A phase II study of venetoclax monotherapy in 30 previously treated patients using 800 mg/day reported 17% VGPR, 63% PR, and 7% MR for an overall response rate of 87%. Response rates were lower in refractory compared with relapsing disease, 57 versus 95%. Dose reductions for adverse events were seen in 2.[62] In an update expanded to 32 patients with a therapy duration of 2 years, the median time to a major response was 5.1 months. The overall, major, and VGPR rates were 84%, 81%, and 19%, respectively. The median

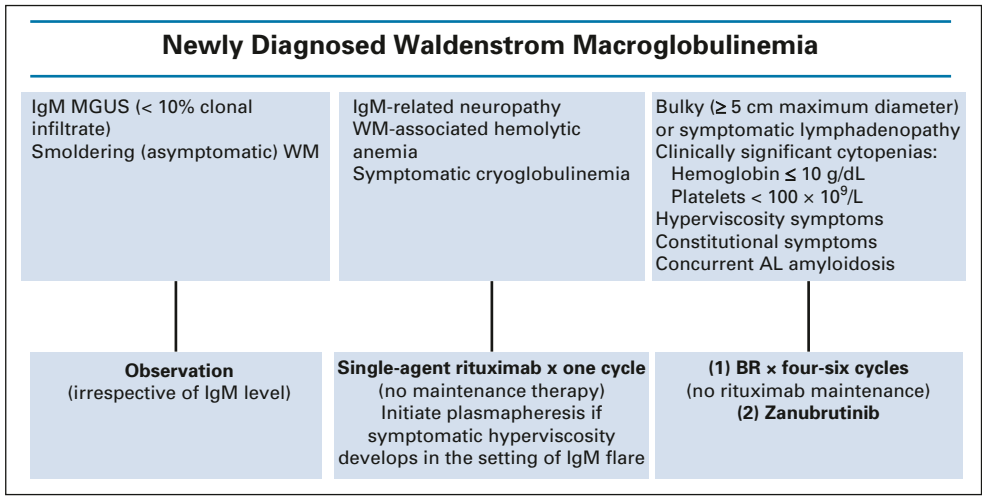

FIG 1. mSMART guidelines for treatment-naive patients with macroglobulinemia. AL, immunoglobulin light chain; BR, bendamustine and rituximab; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenstrom macroglobulinemia.

PFS was 30 months. CXCR 4 mutation did not affect treatment response or PFS. Grade 3 or greater neutropenia was seen in 45%. Venetoclax has high activity in macroglobulinemia both in patients previously exposed and unexposed to ibrutinib. A trial of venetoclax and ibrutinib in newly diagnosed patients with a planned duration of therapy of 2 years is underway (ClinicalTrials.gov identifier: NCT04273139) A 2nd trial comparing ibrutinib and rituximab to ibrutinib, rituximab, and venetoclax with a crossover for patients progressing in the nonvenetoclax arm with limited duration therapy of 24 4-week cycles is accruing (ClinicalTrials.gov identifier: NCT04840602).

STEM-CELL TRANSPLANTATION

With the rapid introduction of highly effective medications for the treatment of macroglobulinemia, the utilization of stem-cell transplantation is in decline. A meta-analysis of 15 trials reported a complete response rate of 22% and relapse rates of 42% at variable reporting intervals. Typical PFS medians are 3 to 4 years[63]; in a registry study of 46 patients receiving autologous stem-cell transplantation, the 3-year OS and PFS were 84.5% and 70.8%, respectively. Others have reported disease-free survival following autologous stem-cell transplant ranging 45%-65% at 5 years.[64] These statistics are not superior to multidrug regimens alluded to above.[65] Currently, autologous stem-

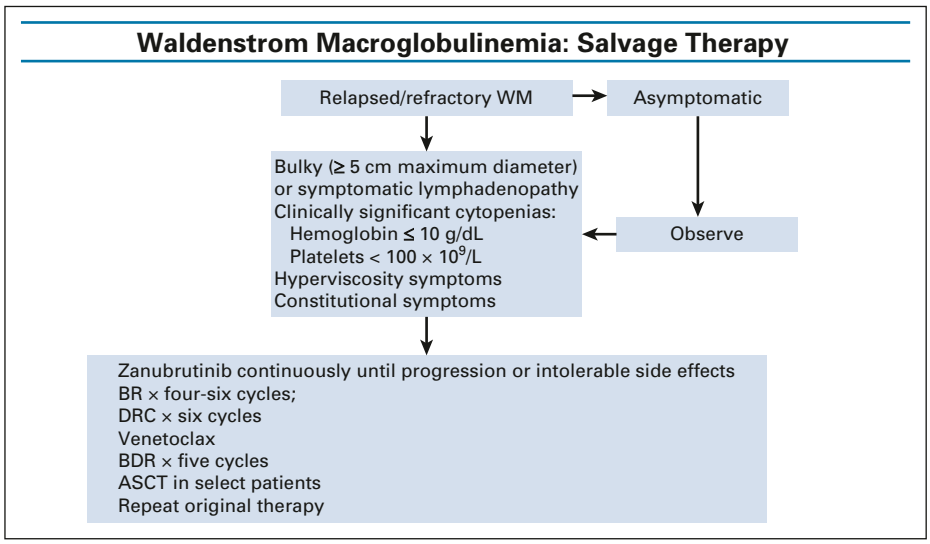

FIG 2. mSMART guidelines for patients with previously treated macroglobulinemia. ASCT, autologous stem-cell transplantation; BDR, bortezomib (weekly, subcutaneously), dexamethasone, and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenstrom macroglobulinemia.

cell transplantation is best reserved for instances where acquisition of modern agents is not feasible.[66]

PUTTING IT ALL TOGETHER

A clinician must ask whether therapy is required. No threshold of IgM should be considered as requiring therapeutic intervention in an otherwise asymptomatic patient. Asymptomatic patients can often be monitored for years, without therapy, sparing them exposure to agents that carry significant toxicity. For patients requiring therapy, phase III trials comparing effective regimens is lacking. This requires cross-trial comparisons that are inaccurate, given the heterogeneity of these patient populations. Other considerations include the patient's comorbidities, drug acquisition costs, preferences regarding oral versus parental therapy, and time-limited versus continuous therapy.

The National Comprehensive Cancer Center publishes guidelines for the treatment of newly diagnosed macroglobulinemia. These consensus recommendations list five preferred regimens for initial therapy but do not place any weight on one regimen over another. It includes rituximab, cyclophosphamide, and dexamethasone, which in a phase III trial was shown to have a much shorter PFS compared with rituximab and bendamustine and carries the risk of alkylating-induced myeloid neoplasm. Although rituximab and bendamustine have been compared with R-CHOP, bendamustine and rituximab has not been compared with dexamethasone, rituximab, and cyclophosphamide directly, and the latter may be a reasonable option. The three options for treatment-naive patients are bortezomib-based, ibrutinib/zanubrutinib-based, and bendamustine-based. There are 10 recommended regimens including single-agent rituximab, which should be considered inferior therapy, and three purine nucleoside analog–based regimens, which should not be considered as part of initial therapy because of the intense immunosuppression that results and the increased risk of subsequent transformation to large-cell lymphoma and therapy-related myeloid neoplasm.

Mayo Clinic mSMART guidelines are consensus recommendations whose principle is if a clinician phones for advice, what would you really tell them. This common scenario resulted in the development of the guidelines. These guidelines (Fig 1) emphasize withholding therapy in asymptomatic patients and limiting rituximab as a single agent to those patients with IgM-mediated peripheral neuropathy and type 2 mixed cryoglobulinemia. For symptomatic patients, there are two major options. Rituximab and bendamustine produces a median response duration of 78 months, is a fixed-duration therapy not exceeding 6 months, and does not require maintenance rituximab. Response rates do not require knowledge of MYD88 or CXCR 4 since they are similar. Primary toxicity is myelosuppression, and the risk of a therapy-related myeloid neoplasm is $< 1\%$ at 6 years. The second option would be zanubrutinib, which carries the advantage of oral therapy with similarly high response rates. The median duration of response has not yet been reached. Therapy is continuous on the basis of currently available data, and there should be no risk of second primary malignancy. On the basis of the Aspen study, diarrhea was seen in 21.8%, hemorrhage in 50.5%, and infection in 69.3%. An Internet search of drug acquisition costs in the United States on February 18, 2022, comparing zanubrutinib for 30 days to bendamustine for 2 days and rituximab-abbs 500 mg dose is virtually identical. This ignores administration costs of parenterally administered medications, monitoring, and all hospital-related costs from therapy-related toxicity. Bendamustine therapy will end at 6 months where BTKi is currently continuous, suggesting cost considerations strongly favor bendamustine until generic BTKi become available.

The decision process for relapsed refractory disease is more complex (Fig 2). The National Comprehensive Cancer Network guidelines list 18 nontransplant recommendations. This is reasonable since following primary treatment failure consideration of more toxic therapies are justified. Important considerations include reutilization of the original regimen if therapy response exceeded 4 years (arbitrary time interval). As an example, if the patient received rituximab and bendamustine for 6 months and then had a 6-year treatment-free interval before progression, repeating this regimen is quite logical. However, if the treatment-free interval was relatively short, consideration of non–cross-resistant salvage is appropriate. If the patient received bendamustine-based therapy with short response, then bortezomib-based, ixazomib-based, or BTKi-based therapy is an appropriate consideration. Cyclophosphamide-based regimens can be considered but they are more toxic than the other regimens. It is likely that venetoclax will rapidly become a preferred second-line regimen, given its ease of use and high response rate. Whether this agent will be given continuously or limited to 2 years awaits the outcome of currently enrolling trials.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Waldenstrom Macroglobulinemia: Tailoring Therapy for the Individual

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