Waldenström Macroglobulinemia

Pashtoon Murtaza Kasi, MD, Stephen M. Ansell, MD, PhD, and Morie A. Gertz, MD, MACP

The authors are affiliated with the Mayo Clinic in Rochester, Minnesota. Dr Kasi is a fellow in the Division of Hematology/Oncology in the Department of Medicine, Dr Ansell is a professor of medicine in the College of Medicine, and Dr Gertz is a professor in the College of Medicine and chair of the Department of Medicine.

Corresponding author:
Morie A. Gertz, MD
Mayo Clinic
200 First St SW
Rochester, MN 55905
E-mail: gertz.morie@mayo.edu
Tel: 507-284-2511
Fax: 507-266-4972

Abstract: Waldenström macroglobulinemia (WM) is an indolent low-grade lymphoma characterized by bone marrow infiltration with lymphoplasmacytic cells associated with a monoclonal immunoglobulin M protein. It is considered incurable. The 5-year survival rate for patients with symptomatic WM is 87% for those with low-risk disease, 68% for those with intermediate-risk disease, and 36% for those with high-risk disease. Owing to recent advances in therapy with new targeted treatment options, relative survival has improved. Insights into mutations in *MYD88* L265P and the WHIM-like *CXCR4* have been shown to be significant not just in terms of their diagnostic and prognostic value, but also as potential targets for therapy. For patients with symptomatic WM, the different classes of agents used to treat WM include alkylating agents (eg, cyclophosphamide and chlorambucil), nucleoside analogues (eg, cladribine and fludarabine) and monoclonal antibodies (eg, rituximab and alemtuzumab). With an increasing number of novel treatment options available including everolimus, bendamustine, bortezomib, ibrutinib, carfilzomib, lenalidomide, and panobinostat, the optimal timing and introduction of these options in the absence of phase 3 trials remains controversial. A treatment algorithm based on Mayo Stratification for Macroglobulinemia and Risk-Adapted Therapy (mSMART) and a comparison of important clinical trials in WM is provided.

Keywords
Bortezomib, everolimus, International Prognostic Scoring System for WM, MYD88, rituximab, Waldenström macroglobulinemia, WHIM-like CXCR4

Background and Definitions

Described first by the Swedish physician Jan G. Waldenström in 1944, Waldenström macroglobulinemia (WM) is an indolent lymphoma characterized by bone marrow infiltration with lymphoplasmacytic cells associated with a monoclonal immunoglobulin M (IgM) protein (Figure 1).[1-3] It is considered incurable.[4,5] The 5-year survival rates for patients with symptomatic WM based on tools used for risk stratification are 87%, 68%, and 36%, respectively, for patients with low-, intermediate-, and high-risk WM.[6] With the increasing number of treatment options available for patients with WM, key considerations for practicing oncologists are which agents to choose and the sequencing of regimens.

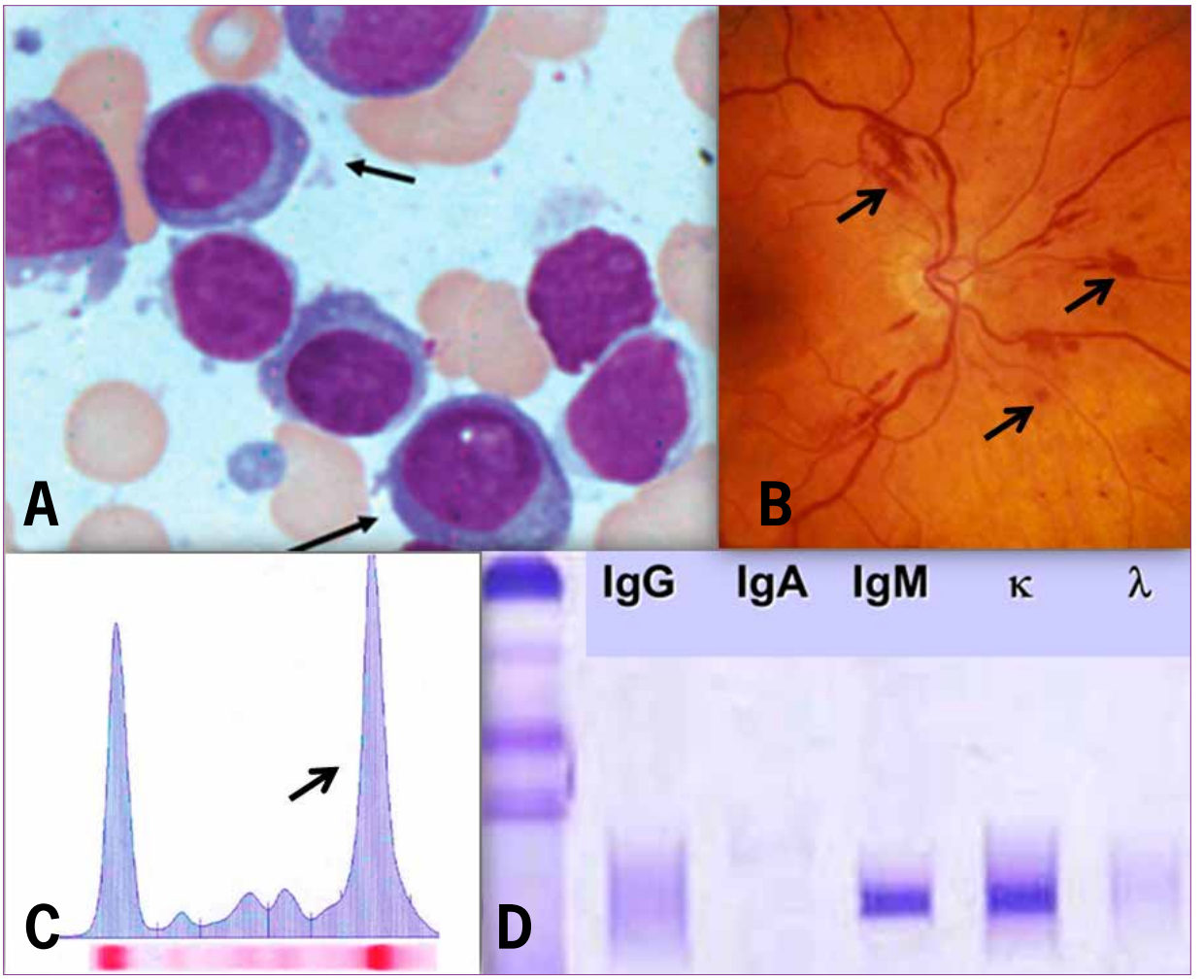

Figure 1. **A,** Bone marrow biopsy showing infiltration by plasma cells (arrow). **B,** WM patient retinopathy showing retinal hemorrhages (arrow) alongside dilated tortuous veins. **C,** Serum protein electrophoresis M-spike (monoclonal gammopathy, arrow). **D,** Immunofixation confirming the monoclonal gammopathy as IgM kappa.

International Prognostic Scoring System

Developed by Morel and colleagues, the International Prognostic Scoring System for Waldenström Macroglobulinemia (ISSWM) helps classify patients with WM into low-risk, intermediate-risk, and high-risk categories.[6] Categorization as noted in Table 1 is based on the presence of 5 covariates identified from a cohort of 587 patients with symptomatic WM.[6] This takes into account the patient's age, as well as 4 laboratory parameters identified as adverse variables. This is the accepted scoring system, which has been validated by other studies.[7]

Serum lactate dehydrogenase, which is an important prognostic marker for follicular and large-cell lymphomas, is not part of the prognostic scoring system for WM. Serum lactate dehydrogenase may add to prognostication among those patients with high-risk WM, according to the ISSWM. Age is a powerful predictor of outcomes; being older than 65 years automatically places the patient into an intermediate- or high-risk category.

Table 1. International Prognostic Scoring System for Waldenström Macroglobulinemia[6]

Adverse Characteristics
Age >65 y
Hemoglobin ≤11.5 g/dL
Platelet count ≤100 × 109/L
β_2-microglobulin >3 mg/L
Monoclonal IgM concentration >7.0 g/dL
Low risk: Age <65 y and 0 or 1 adverse characteristics Intermediate risk: Age >65 y or 2 adverse characteristics High risk: More than 2 adverse characteristics

IgM, immunoglobulin M; y, years.

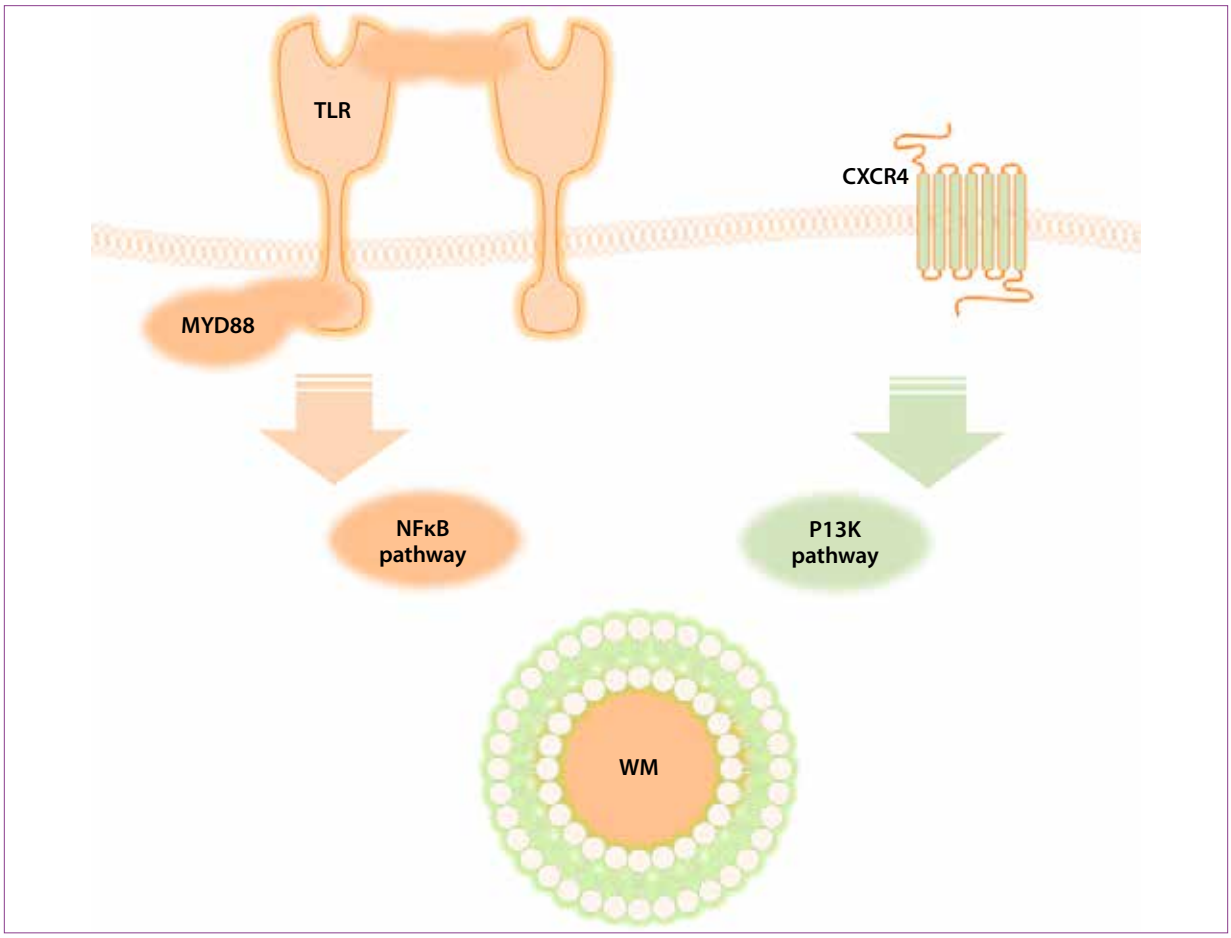

Figure 2. Schematic diagram outlining the important common somatic mutations in WM (*MYD88* and *CXCR4*). In simplistic terms, MYD88 works through Toll-like receptors to activate the NFκB pathway, whereas CXCR4 is a chemokine receptor functioning through the PI3K pathway.

NFκB, nuclear factor κB; PI3K, phosphatidylinositol 3-kinase; TLR, Toll-like receptor; WM, Waldenström macroglobulinemia.

Response Criteria

For the purpose of this review, we have used the definition of overall response as a partial response or better (decline in IgM ≥50%) for consistency and comparison across studies. Response is a predictor of both relapse-free and overall survival.

Prevalence and Risk Factors

WM is a rare disease. According to the Surveillance, Epidemiology, and End Results database, there were a total of 1835 new cases reported over 2 decades.[8] This is an incidence of 0.38 per 100,000 persons per year. Overall, there has been a rising age-adjusted incidence over time.[9]

WM is twice as common in men as in women.[8] The incidence also is higher in older age groups (median age of 73 years in whites).[8] The incidence in black Americans is half that of white Americans, with a median age in blacks of 63 years. Older age, black race, and male sex were associated with poorer prognosis.[9] Similar findings have been reported across other population-based studies and databases.[10-12] The relative survival has improved in the decade from 2000 to 2010.[8,9,11]

Clinical Presentation

The spectrum of clinical presentation of patients in WM can be divided into 2 groups. The first is related to the cytopenias from infiltration of the bone marrow, and the second is related to hyperviscosity from the IgM gammopathy.[2] Hyperviscosity (measured in centipoise; normal is ≤1.8) can present subtly as mild headaches and visual disturbances, or severely as seizures and coma.[4] Other signs and symptoms include fatigue, sensory neuropathy, and epistaxis.[8] Splenomegaly and lymphadenopathy are relatively uncommon.[13] Autoimmune

Table 2. Cytogenetic Abnormalities and Somatic Mutations Reported in Patients With Waldenström Macroglobulinemia[19,24,26]

Cytogenetics	Mutations
Deletion of long arm (q) of chromosome 6	*MYD88* (90%)
Deletion 13q14	*CXCR4* (30%)
Deletion 17p13	
Trisomy 4	
Gain in the short arm (p) of chromosome 6	

hemolytic anemia (cold agglutinin disease) also can be seen. Other clinical associations include those related to associated cryoglobulinemias and/or amyloidosis.[14-16] Schnitzler syndrome (a rare disease characterized by chronic urticarial rash) has been reported.[17]

Biological Insights

MYD88 L265P and WHIM-Like CXCR4 Mutations

Somatic mutations in *MYD88* L265P and the WHIM-like *CXCR4* are common findings in patients with WM and have implications for the pathogenesis and outcome of patients with WM (Figure 2).[18,19,20] *MYD88* mutations are seen in more than 90% of patients with WM, and *CXCR4* mutations are seen in up to 30% of patients.[21] The particular type (frameshift, nonsense) and combination of the mutations seen in patients with WM impacts the clinical presentation and offers insights into prognosis and potential drug resistance.[22,23]

Other Cytogenetic Abnormalities and Findings

The cytogenetic abnormalities and somatic mutations reported in patients with WM[24] are outlined in Table 2. Other gene polymorphisms of predictive potential include the expression of the *hCNT1* gene.[4,25] In a phase 2 study, human concentrative nucleoside transporter 1 (hCNT1) was predictive of response to cladribine. Deletion of the long arm of chromosome 6 can be seen in more than one-third of the patients, but does not appear to affect prognosis or survival.[26] The monoclonal antibodies rituximab (Rituxan, Genentech/Biogen Idec) and alemtuzumab are active in patients with WM.[27] Specific polymorphisms in the FcγRIIIA (CD16) receptor have been shown to be predictive of response to rituximab in patients with WM.[28,29] Genome-wide expression studies of these tumors demonstrate an expression pattern closer to that of chronic lymphocytic leukemia than to that of multiple myeloma.[30] In a large population-based study from Sweden, patients with IgM monoclonal gammopathy of unknown significance had a 5-fold increased risk of developing chronic lymphocytic leukemia, suggesting a common pathogenesis.[31]

Table 3. Tests to Be Considered as Part of Workup and Staging of Waldenström Macroglobulinemia

Complete blood count
Serum creatinine
Serum calcium level
Serum albumin level
Serum protein electrophoresis
Serum IgM monoclonal protein level
M-spike
β_2-microglobulin
Serum-free light chains[a]
CT scan of chest/abdomen/pelvis for evaluation of adenopathy
PET/CT[a]

IgM, immunoglobulin M; CT, computed tomography; PET, positron emission tomography.

[a] Role in evaluation of WM is questionable at this time.

General Approach to Patient Evaluation

Table 3 outlines the tests to be considered as part of evaluating a new patient with WM. Serum monoclonal protein level and bone marrow involvement are key.[32] Computed tomography (CT) scans are used for the assessment of adenopathy if clinically indicated. Positron emission tomography (PET)/CT scans have the potential to offer further information about patients with WM, based on limited case series.[32] At present, however, routine use of ^{18}F-fluorodeoxyglucose-PET/CT imaging is not recommended and warrants further evaluation.[32,33]

Key Considerations Regarding Natural History and Clinical Management

When WM Should Go Untreated

Observation is an appropriate option for patients diagnosed in the absence of symptoms. If the patient is asymptomatic, an arbitrary IgM number should not trigger initiation of chemotherapy. Symptoms created by progressive cytopenias, constitutional complaints, and hyperviscosity syndrome require therapy.

Factors Influencing Choice and Timing of Treatment

A number of factors influence the choice and timing of a particular treatment regimen. The overall goal is to alleviate symptoms.[4] The 4 most common symptoms requiring intervention are hyperviscosity, constitutional/B symptoms, bulky disease, and cytopenias.[34] The ISSWM system can stratify patients into low-risk, intermediate-risk, and high-risk categories. A treatment algorithm is presented in Figure 3 based on a provider consensus statement available

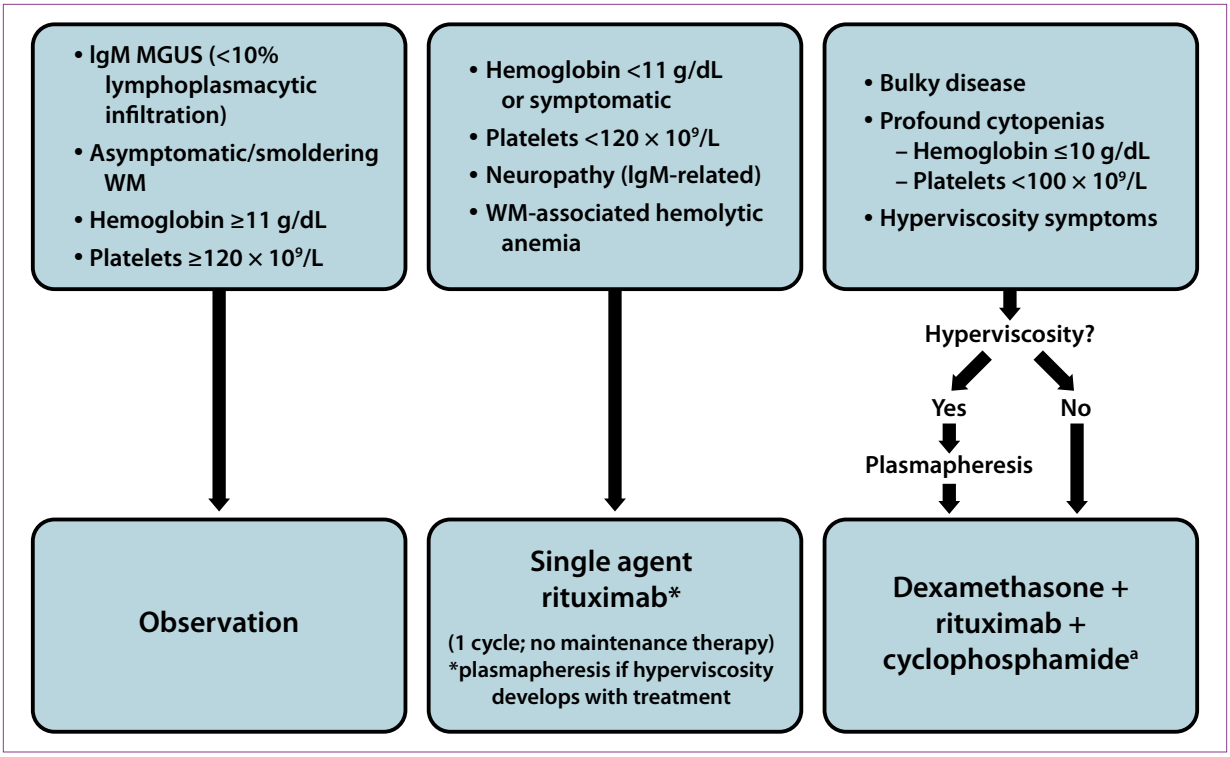

Figure 3. The risk-adapted approach to management of multiple myeloma and related disorders: Mayo Stratification for Macroglobulinemia and Risk-Adapted Therapy (mSMART).

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of unknown significance; WM, Waldenström macroglobulinemia.

[a] Bendamustine plus rituximab is an alternative.

Updated from Ansell SM et al. *Mayo Clin Proc*. 2010;85(9):824-33.[34]

through Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART).[34]

Indications for Plasmapheresis

The usual indications for plasma exchange used by clinicians are compatible symptoms such as oronasal bleeding with an IgM of more than 5000 mg/dL or a laboratory cutoff viscosity of 3.5 or greater.[35] This is more of a guideline and it is important to take into account the patient's comorbidities and severity of hyperviscosity symptoms. As an example, blurred vision due to retinal hemorrhage requires urgent plasma exchange to preserve vision. Some patients may continue to be asymptomatic beyond these cutoffs and will not require therapy.

Treatment Options

Asymptomatic WM

Patients without any symptoms generally are followed every 3 to 6 months with blood count and protein measurements. Asymptomatic patients with smoldering WM and a low burden of disease can be followed for years before treatment may be warranted.[36]

Symptomatic WM, First-Line Treatment

More than two-thirds of patients are symptomatic at the time of their diagnosis.[37] For patients with symptomatic WM, the different classes of agents used to treat WM include alkylating agents (eg, cyclophosphamide and chlorambucil), nucleoside analogues (NAs; eg, cladribine and fludarabine), monoclonal antibodies (eg, rituximab and alemtuzumab), and novel agents (eg, bortezomib, carfilzomib [Kyprolis, Onyx], and lenalidomide [Revlimid, Celgene]). Depending on the clinical situation and the overall goals of treatment, the chemotherapeutic agents and/or monoclonal antibodies can be used singly or in combination with each other.[11,38] There are, however, very few randomized trials to help guide the initial choice of treatment.[39,40] Table 4 outlines selected studies using chemoimmunotherapy combination regimens in patients with WM.

When comparing the studies outlined in Table 4, there are several things to keep in mind. First, the age of patients selected for participation varies. Studies with patients whose median age is higher are likely to have lower response rates, time to progression, and overall survival compared with studies conducted in a younger population. A study conducted in untreated patients would be expected to demonstrate

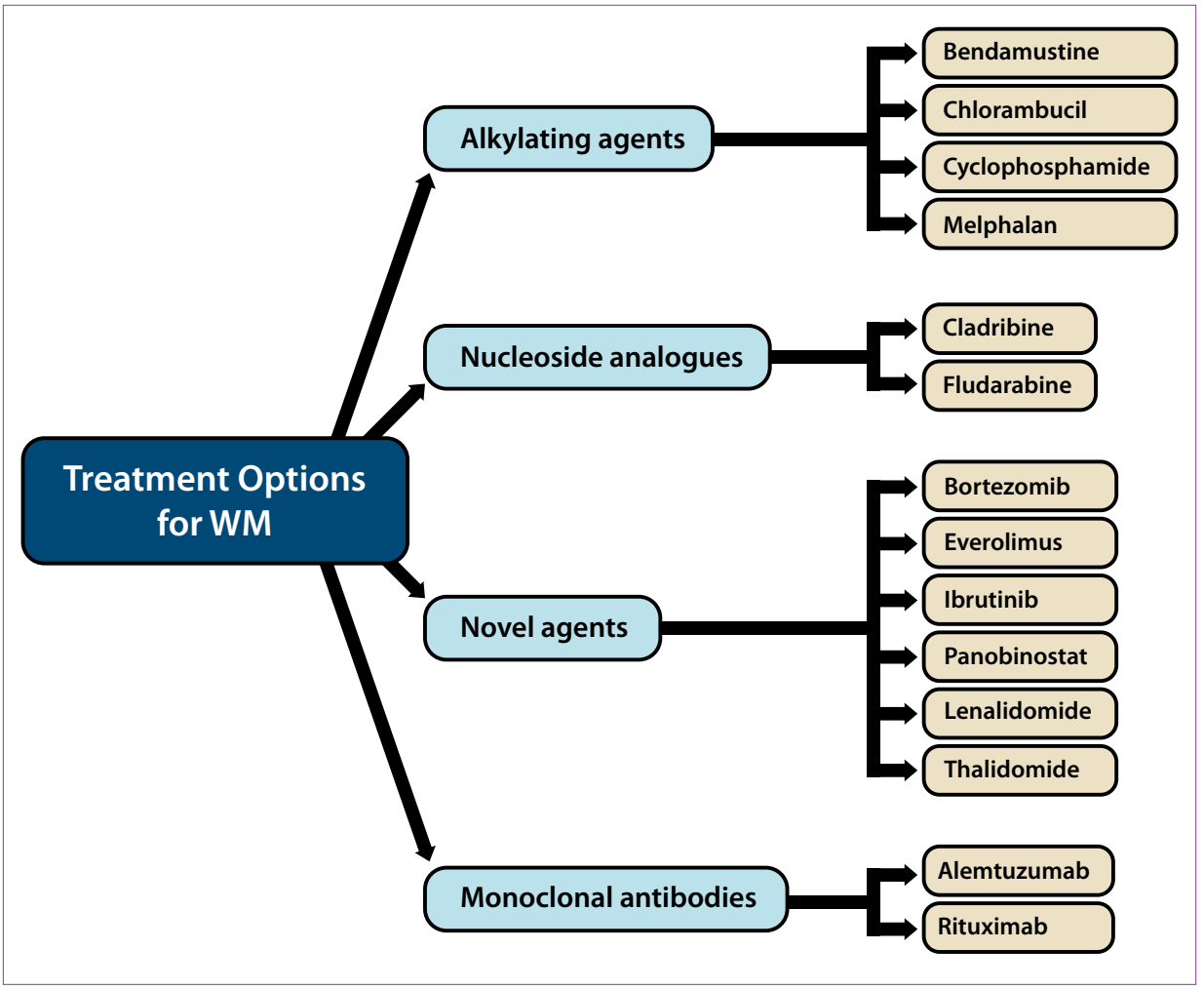

Figure 4. Classes of agents used in the treatment of Waldenström macroglobulinemia.

better outcomes than one in those who have received prior treatments. The median follow-up for most of these studies is approximately 2 years; long-term follow-up often is lacking. The true overall survival and progression-free survival therefore are subject to variability. Finally, many of the studies are small phase 2 trials or retrospective cohorts, making an accurate comparison between different treatments difficult.

One of the largest randomized controlled trials was reported by Leblond and colleagues in 339 patients with WM.[39] The trial, which compared fludarabine with chlorambucil, showed a statistically significant improvement in OS in patients receiving fludarabine. The median OS was not reached for the fludarabine arm, and was 69.8 months (95% CI, 61.6-79.8 months) for patients receiving chlorambucil; *P*=.014). Median PFS in the same study was noted to be 37.8 vs 27.1 months, respectively.

Single-agent rituximab is well tolerated, but produces a partial response in only 55% of patients, making it inferior to multidrug combinations (Table 4).[41-43] Drug combinations such as thalidomide/rituximab,[29,44] bortezomib (Velcade, Millennium Pharmaceuticals)/rituximab, carfilzomib/rituximab, and bendamustine (Treanda, Teva)/rituximab have shown excellent results.[45-47]

Considerations When Treating WM Patients With Rituximab. One risk of treating patients with rituximab-based regimens is the IgM flare, also called the rituximab flare. First described by Dimopoulos and colleagues, it refers to the sharp increase in the IgM levels and/or symptoms associated with it.[29,42,48] Postulated mechanisms behind the IgM flare include rituximab-induced B-cell signaling that may lead to a transient rise after treatment with rituximab.[48] It does not reflect treatment failure and for most of the patients, a decline in IgM levels is seen within the next several months of therapy.[49] In the initial case descriptions, the initial paradoxical increases in serum IgM levels and the concomitant rise in viscosity lead to clinically significant events, including subdural hemorrhage, worsening

headaches, and/or epistaxis.[48] IgM flare is seen in more than half of the patients treated with rituximab alone, and in up to 30% of patients treated with rituximab-based combination regimens.[1,5,36] The reported rates are lower in some of the combination regimens of rituximab with an NA.[50] When using rituximab as part of a combination regimen, delaying it to the second cycle or giving it at the same time as chemotherapy may be safer than giving it alone.[51] In general, an increase in IgM levels of more than 25% during treatment may warrant consideration of plasmapheresis in patients with IgM levels of greater than 5000 mg/dL.[35,44,48]

Usual Time to Best Response in Patients With WM. Depending on the choice of agent, the usual time to reduction in the monoclonal protein is on the order of months.[13,50] There is, however, an ongoing response (best response) noted subsequently.[38,45,52] Responses are seen sooner with novel agents than with alkylators or purine analogues.[53]

In studies using only rituximab, it often took a year to achieve the best response after the initial objective or minor response in 1 study and up to 17 months in another.[43,54] Similarly, the median time to best response in patients receiving the bortezomib, dexamethasone, and rituximab (BDR) combination regimen was more than 15 months.[35]

Symptomatic WM, Relapsed/Refractory Disease

Relapsed and/or refractory disease confers a poorer prognosis when compared with patients with untreated WM (Table 4). Other treatment regimens are selected based on the agents that the patient has already been treated with and the patient's age and comorbidities (Figure 4). Bortezomib and rituximab in patients with WM[5,45] produces an overall response (at least a partial response) in 65% of untreated patients and 51% of treated patients. Responses often are not durable.[5,45] In patients treated with rituximab, the 5-year overall response rate has been noted to be 85% in untreated patients vs 48% in previously treated patients.[54] Exposure of patients to NAs should be avoided in patients who may be considered candidates for autologous stem cell transplantation (ASCT), given problems with stem cell mobilization.[36,37,55]

Novel Targeted Therapies and Regimens

Over the past decade, numerous novel agents have been identified that have shown activity in patients with WM (Table 4). The studies have demonstrated high levels of activity in both untreated patients and patients with relapsed/refractory WM.[56,57] As noted in Table 4, the response rate varies from 20% to 70% for most of the novel targeted therapies used as single agents.[56] The higher responses seen are in the untreated WM setting.[1,54,58] Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, shows significant activity in patients with relapsed WM.[2] Counting both partial responses (50%) and minor responses (23%), the overall clinical benefit rate was shown to be 73% in one study.[2]

Agents active in patients with multiple myeloma have shown activity in patients with WM and have been incorporated into treatment.[59] The Bruton's tyrosine kinase inhibitor ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) shows activity in WM. Data presented at the 2013 annual meeting of American Society of Hematology showed a major response rate of 57.1% in the relapsed/refractory setting. The drop in IgM levels as well as the improvement in hematologic parameters occurred rapidly.[60] Novel agents offer activity and durable responses in WM with a good safety profile compared with many traditional chemotherapy regimens, making them a viable treatment option.[56,61]

Side Effects of Therapies Used in WM

The toxicity profiles of combination regimens and of novel agents are a consideration in the choice of treatment for patients with WM. Side effects can be divided into short-term and long-term. Patients treated with more of the traditional chemotherapies experience higher rates of cytopenias and myelosuppression compared with those treated with monoclonal antibodies and/or novel agents.[62] Patients exposed to NAs are at slightly increased risk for developing myelodysplastic syndromes/acute myeloid leukemias.[37,40] NAs also may affect stem cell mobilization if ASCT is a consideration. Rituximab, one of the most commonly used monoclonal antibodies, generally is well tolerated.[41] Patients treated with immunomodulatory agents such as thalidomide and lenalidomide can develop cumulative worsening neuropathies and an increase in anemia.[29,44] Bortezomib can produce a high rate of peripheral neuropathy[1,5]; carfilzomib has a much lower incidence of peripheral neuropathy.[47] Usage of the proteasome inhibitors in combination regimens is associated with a high incidence of herpes zoster, warranting antiviral prophylaxis.[35]

The mTOR inhibitor everolimus has metabolic side effects, resulting in elevations of triglycerides and blood sugar. This does not require dose reduction for most patients. Lung toxicity with everolimus is rarely life-threatening, and generally manifests as an immune-mediated noninfectious pneumonitis.[63] Patients may be asymptomatic or present with a dry cough. Imaging studies, including a CT scan, demonstrate ground-glass opacities requiring discontinuation of the drug. Corticosteroids are used in treating this pneumonitis after infectious causes of lung toxicity are ruled out.

Role of Stem Cell Transplantation

There are a limited number of studies addressing the question of autologous stem cell transplantation in patients with WM (Table 4).[37,52,64,65] A review article published in 2012 examined data on the safety and efficacy of autologous stem cell transplantation and durability of responses.[64] Autologous

Table 4. Studies of Treatment Regimens and Novel Agents Used in the Treatment of Waldenström Macroglobulinemia

Author	Treatment	N	Median Age, y	Setting	ORR[a]	PFS	OS
Cytotoxic chemotherapy regimens							
Treon,[35] 2009	Bortezomib/dexamethasone/rituximab	23	66	Untreated	83%	NR Exceeds 30 mo	NR
Dimopoulos,[1] 2013	Bortezomib/dexamethasone/rituximab	59	70	Untreated	70%	42 mo	82% 3-y survival
Treon,[47] 2014	Carfilzomib/rituximab/dexamethasone	31	61	90.3% untreated	87.1%	NR	No deaths reported
Tedeschi,[50] 2011	Fludarabine/cyclophosphamide/rituximab	43	65	65% untreated	74.4%	—	69.1% at 4 y
Dimopoulos,[36] 2007	Dexamethasone/rituximab/cyclophosphamide	72	69	Untreated	74%	2-y PFS 67%	78% 2-y survival
Dimopoulos[53]	Fludarabine/cyclophosphamide	11	73	18% untreated 2 (18%) relapses 7 (64%) refractory	55%	TTP 24 mo	70% 2-y survival
Leblond,[39,c] 2013	Fludarabine vs chlorambucil	167 vs 165	68	Untreated	45.6% vs 35.9%	37.8 mo vs 27.1 mo	NR vs 69.8 mo
Leblond,[40,c] 2001	Fludarabine vs cyclophosphamide/doxorubicin/prednisone	45 vs 45	64	Relapsed/refractory 50 (54%) relapses 42 (46%) refractory	30% vs 11%	19 mo vs 3 mo	41 mo vs 45 mo
Dhodapkar[13]	Fludarabine	182	33% >70 y	64.8% untreated	36%	5-y PFS 41%	Estimated OS at 5 y was 58%
Hellmann,[62] 1999	Cladribine	22	62	41% untreated	40.9%	— Mean duration of response 12 mo	— 7 deaths reported; mean OS 36 mo
Liu[67]	Cladribine	20	66	57% untreated	55%	— 1 relapse in responders at 18 mo	86% at 4 y
Rituximab-based doublet combination therapies							
Treon,[51] 2009	Fludarabine/rituximab	43	61	63% untreated	86%	TTP 51.2 mo	— 2 deaths reported
Laszlo,[4] 2011	Cladribine/rituximab	29		55.1% untreated	79.3%	NR 4 relapses at 50 mo	NR
Treon,[46] 2011	Bendamustine/rituximab	30	68	Relapsed/refractory Relapsed, 47% Refractory, 53%	83.3%	TTP 13.2 mo	— 1 reported death due to transformation
Ghobrial,[5] 2010	Bortezomib/rituximab	26	63	Untreated	65%	NR 6 pt progressed at 14 mo	NR Estimated 1-y OS of 96%
Ghobrial,[45] 2010	Bortezomib/rituximab	37	64	Relapsed/refractory >1 therapies (70%)	51%	15.6 mo (18 pt progressed at 16 mo)	NR Estimated 1-y OS of 94%
Treon,[29] 2008	Thalidomide/rituximab	25	62	80% untreated	64%	TTP 34.8 mo	— 2 unrelated deaths

Treon,[44,b] 2009	Lenalidomide/rituximab	16	65	75% untreated	25%	TTP 17.1 mo	—
Single-agent rituximab							
Dimopoulos,[42] 2002	Rituximab	27	72	56% untreated	44%	TTP 16 mo	—
Treon,[43] 2005	Rituximab	29	65	42% untreated 3 (10%) relapses 14 (48%) refractory	48.3%	TTP 14 mo	— 1 unrelated death
Gertz,[54] 2009	Rituximab	69	66	49.2% untreated	32%	23.1 mo	66% at 5 y
Novel single agents							
Ghobrial,[2] 2014	Everolimus	60	64	Relapsed	50%	21 mo	NR
Treon,[58] 2011	Alemtuzumab	28	59.5	17% untreated 11 (36%) relapses 12 (43%) refractory	36%	TTP 14.5 mo	— 4 deaths reported
Treon,[66] 2007	Bortezomib	27	62	Relapsed/refractory 12 (44%) relapses 15 (56%) refractory	48.1%	TTP 6.6 mo	— 1 death reported
Chen[61]	Bortezomib	27	65	44% untreated	44%	16.3 mo	—
Treon,[60] 2013	Ibrutinib	63	63	Relapsed/refractory 46 (73%) relapses 17 (27%) refractory	57.1%	—	—
Ghobrial,[56] 2013	Panobinostat	36	62	Relapsed/refractory	22%	6.6 mo	—
Ghobrial,[68] 2010	Perifosine	37	65	>1 therapies (68%)	11%	12.6 mo	26 mo
Dimopoulos,[59] 2001	Thalidomide	20	72	50% untreated	25%	TTP 4 mo	— 2 deaths reported
Select studies on ASCT and AlloSCT							
Kyriakou,[37] 2010	ASCT	155	53	<3 therapies 68% ≥3 therapies 32%	89%	61.7% at 3 y 39.7% at 5 y	Estimated OS at 5 y was 77%
Garnier[52]	AlloSCT	24	48	Median of 3 lines of therapy	91%	58% at 5 y	Estimated OS at 5 y was 67%
Dreger[69]	26 AlloSCT 10 ASCT	36	49 56	≥3 therapies 52.7%	58%[d]	31% at 3 y 65% at 3 y	46% at 3 y 70% at 3 y

AlloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; mo, months; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pts, patients; TTP, time to progression; y, year/years.

[a] Partial response or better.

[b] Discontinuation of lenalidomide occurred in 14 of the 16 patients owing to worsening anemia in these patients, which led to the study being stopped.

[c] Randomized controlled trial.

[d] 10 (28%) patients died prior to day 100 after transplant; their responses therefore could not be assessed.

stem cell transplantation is a viable option in patients at the time of relapse if they retain chemotherapy sensitivity. The target population would generally be young patients at early relapse.[37,64] Stem cell transplantation also is a viable treatment consideration for countries where not all novel treatments may be available. The use of allogeneic stem cell transplantation should be limited to clinical trial settings.[64]

Monitoring

Patients with WM are followed every 3 to 6 months, with blood work as shown in Table 3 and scans if needed. Patients may have discordant responses between the IgM level and the degree of marrow infiltration.[66] Because the markers in WM are generally surrogates of the disease burden, repeat bone marrow biopsies are not needed.

The Road Ahead

Studies suggest that combining novel agents, such as histone deacetylase inhibitors and proteasome inhibitors, holds promise in multiple myeloma.[47,56] The data on everolimus, including its long-term tolerability, make it a reasonable new treatment option for WM.[2] Newer biological insights into *MYD88* and WHIM-like *CXCR4* have been significant and intriguing not just in terms of their diagnostic and prognostic value, but also as potential targets for therapy in patients with WM.

Disclosures

Drs Kasi and Ansell have reported no relevant financial relationships. Dr Gertz has disclosed financial relationships with Onyx, Celgene, Novartis, and Millennium.

References

1. Dimopoulos MA, García-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood*. 2013;122(19):3276-3282.
2. Ghobrial IM, Witzig TE, Gertz M, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia. *Am J Hematol*. 2014;89(3):237-242.
3. Waldenström JG. Macroglobulinemia—a review. *Haematologica*. 1986;71(6):437-440.
4. Laszlo D, Andreola G, Rigacci L, et al. Rituximab and subcutaneous 2-chloro-2'-deoxyadenosine as therapy in untreated and relapsed Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):130-132.
5. Ghobrial IM, Xie W, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenström Macroglobulinemia. *Am J Hematol*. 2010;85(9):670-674.
6. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood*. 2009;113(18):4163-4170.
7. Dimopoulos MA, Kastritis E, Delimpassi S, Zomas A, Kyrtsonis MC, Zervas K. The International Prognostic Scoring System for Waldenstrom's macroglobulinemia is applicable in patients treated with rituximab-based regimens. *Haematologica*. 2008;93(9):1420-1422.
8. Wang H, Chen Y, Li F, et al. Temporal and geographic variations of Waldenstrom macroglobulinemia incidence: a large population-based study. *Cancer*. 2012;118(15):3793-3800.
9. Castillo JJ, Olszewski AJ, Cronin AM, Hunter ZR, Treon SP. Survival trends in Waldenström macroglobulinemia: an analysis of the Surveillance, Epidemiology and End Results database. *Blood*. 2014;123(25):3999-4000.
10. Kristinsson SY, Eloranta S, Dickman PW, et al. Patterns of survival in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia: a population-based study of 1,555 patients diagnosed in Sweden from 1980 to 2005. *Am J Hematol*. 2013;88(1):60-65.
11. Kristinsson SY, Bjorkholm M, Landgren O. Survival in monoclonal gammopathy of undetermined significance and Waldenstrom macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2013;13(2):187-190.
12. Phekoo KJ, Jack RH, Davies E, Møller H, Schey SA; South Thames Haematology Specialist Committee. The incidence and survival of Waldenström's Macroglobulinaemia in South East England. *Leuk Res*. 2008;32(1):55-59.
13. Dhodapkar MV, Jacobson JL, Gertz MA, et al. Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood*. 2001;98(1):41-48.
14. Néel A, Perrin F, Decaux O, et al. Long-term outcome of monoclonal (type 1) cryoglobulinemia. *Am J Hematol*. 2014;89(2):156-161.
15. Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2009;114(12):2375-2385.
16. Palladini G, Merlini G. Diagnostic challenges of amyloidosis in Waldenstrom macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2013;13(2):244-246.
17. Lipsker D. The Schnitzler syndrome. *Orphanet J Rare Dis*. 2010;5(1):38.
18. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. *Blood*. 2014;123(18):2791-2796.
19. Cao Y, Hunter ZR, Liu X, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's Macroglobulinemia [published online June 10, 2014]. *Leukemia*. doi:10.1038/leu.2014.187.
20. Treon SP, Hunter ZR, Castillo JJ, Merlini G. Waldenström macroglobulinemia. *Hematol Oncol Clin North Am*. 2014;28(5):945-970.
21. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood*. 2014;123(11):1637-1646.
22. Ondrejka SL, Lin JJ, Warden DW, Durkin L, Cook JR, Hsi ED. MYD88 L265P somatic mutation: its usefulness in the differential diagnosis of bone marrow involvement by B-cell lymphoproliferative disorders. *Am J Clin Pathol*. 2013;140(3):387-394.
23. Lenz G. Waldenstrom macroglobulinemia: genetics dictates clinical course. *Blood*. 2014;123(18):2750-2751.
24. Nguyen-Khac F, Lambert J, Chapiro E, et al; Groupe Français d'Etude de la Leucémie Lymphoïde Chronique et Maladie de Waldenström (GFCLL/MW); Groupe Ouest-Est d'étude des Leucémie Aiguës et Autres Maladies du Sang (GOELAMS); Groupe d'Etude des Lymphomes de l'Adulte (GELA). Chromosomal aberrations and their prognostic value in a series of 174 untreated patients with Waldenström's macroglobulinemia. *Haematologica*. 2013;98(4):649-654.
25. Rabascio C, Laszlo D, Andreola G, et al. Expression of the human concentrative nucleotide transporter 1 (hCNT1) gene correlates with clinical response in patients affected by Waldenström's Macroglobulinemia (WM) and small lymphocytic lymphoma (SLL) undergoing a combination treatment with 2-chloro-2′-deoxyadenosine (2-CdA) and Rituximab. *Leuk Res*. 2010;34(4):454-457.
26. Chang H, Qi C, Trieu Y, et al. Prognostic relevance of 6q deletion in Waldenström's macroglobulinemia: a multicenter study. *Clin Lymphoma Myeloma*. 2009;9(1):36-38.
27. Owen RG, Hillmen P, Rawstron AC. CD52 expression in Waldenstrom's macroglobulinemia: implications for alemtuzumab therapy and response assessment. *Clin Lymphoma*. 2005;5(4):278-281.
28. Treon SP, Hansen M, Branagan AR, et al. Polymorphisms in FcgammaRIIIA (CD16) receptor expression are associated with clinical response to rituximab in Waldenström's macroglobulinemia. *J Clin Oncol*. 2005;23(3):474-481.
29. Treon SP, Soumerai JD, Branagan AR, et al. Thalidomide and rituximab in Waldenstrom macroglobulinemia. *Blood*. 2008;112(12):4452-4457.
30. Chng WJ, Schop RF, Price-Troska T, et al. Gene-expression profiling of Waldenstrom macroglobulinemia reveals a phenotype more similar to chronic lymphocytic leukemia than multiple myeloma. *Blood*. 2006;108(8):2755-2763.
31. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. *Blood*. 2009;114(4):791-795.
32. Banwait R, O'Regan K, Campigotto F, et al. The role of 18F-FDG PET/CT imaging in Waldenstrom macroglobulinemia. *Am J Hematol*. 2011;86(7):567-572.
33. Owen RG, Kyle RA, Stone MJ, et al; VIth International Workshop on Waldenström macroglobulinaemia. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol*. 2013;160(2):171-176.
34. Ansell SM, Kyle RA, Reeder CB, et al. Diagnosis and management of Waldenström macroglobulinemia: Mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines. *Mayo Clin Proc*. 2010;85(9):824-833.
35. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *J Clin Oncol*. 2009;27(23):3830-3835.
36. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol*. 2007;25(22):3344-3349.
37. Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28(13):2227-2232.
38. Peinert S, Tam CS, Prince HM, et al. Fludarabine based combinations are highly effective as first-line or salvage treatment in patients with Waldenström macroglobulinemia. *Leuk Lymphoma*. 2010;51(12):2188-2197.
39. Leblond V, Johnson S, Chevret S, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. *J Clin Oncol*. 2013;31(3):301-307.

40. Leblond V, Lévy V, Maloisel F, et al; French Cooperative Group on Chronic Lymphocytic Leukemia and Macroglobulinemia. Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood*. 2001;98(9):2640-2644.
41. Kasi PM, Tawbi HA, Oddis CV, Kulkarni HS. Clinical review: Serious adverse events associated with the use of rituximab - a critical care perspective. *Crit Care*. 2012;16(4):231.
42. Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol*. 2002;20(9):2327-2333.
43. Treon SP, Emmanouilides C, Kimby E, et al. Extended rituximab therapy in Waldenstrom's macroglobulinemia. *Ann Oncol.* 2005;16(1):132-138.
44. Treon SP, Soumerai JD, Branagan AR, et al. Lenalidomide and rituximab in Waldenstrom's macroglobulinemia. *Clin Cancer Res.* 2009;15(1):355-360.
45. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. *J Clin Oncol*. 2010;28(8):1422-1428.
46. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma Leuk.* 2011;11(1):133-135.
47. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. *Blood*. 2014;124(4):503-510.
48. Treon SP, Branagan AR, Hunter Z, Santos D, Tournhilac O, Anderson KC. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. *Ann Oncol.* 2004;15(10):1481-1483.
49. Ghobrial IM, Fonseca R, Greipp PR, et al; Eastern Cooperative Oncology Group. Initial immunoglobulin M 'flare' after rituximab therapy in patients diagnosed with Waldenstrom macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer*. 2004;101(11):2593-2598.
50. Tedeschi A, Benevolo G, Varettoni M, et al. Fludarabine plus cyclophosphamide and rituximab in Waldenstrom macroglobulinemia: an effective but myelosuppressive regimen to be offered to patients with advanced disease. *Cancer*. 2012;118(2):434-443.
51. Treon SP, Branagan AR, Ioakimidis L, et al. Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia. *Blood*. 2009;113(16):3673-3678.
52. Garnier A, Robin M, Larosa F, et al. Allogeneic hematopoietic stem cell transplantation allows long-term complete remission and curability in high-risk Waldenström's macroglobulinemia. Results of a retrospective analysis of the Société Française de Greffe de Moelle et de Thérapie Cellulaire. *Haematologica*. 2010;95(6):950-955.
53. Dimopoulos MA, Hamilos G, Efstathiou E, et al. Treatment of Waldenstrom's macroglobulinemia with the combination of fludarabine and cyclophosphamide. *Leuk Lymphoma*. 2003;44(6):993-996.
54. Gertz MA, Abonour R, Heffner LT, Greipp PR, Uno H, Rajkumar SV. Clinical value of minor responses after 4 doses of rituximab in Waldenström macroglobulinaemia: a follow-up of the Eastern Cooperative Oncology Group E3A98 trial. *Br J Haematol*. 2009;147(5):677-680.
55. Treon SP, Hunter Z, Barnagan AR. CHOP plus rituximab therapy in Waldenstrom's macroglobulinemia. *Clin Lymphoma*. 2005;5(4):273-277.
56. Ghobrial IM, Campigotto F, Murphy TJ, et al. Results of a phase 2 trial of the single-agent histone deacetylase inhibitor panobinostat in patients with relapsed/refractory Waldenström macroglobulinemia. *Blood*. 2013;121(8):1296-1303.
57. Gertz MA, Rue M, Blood E, Kaminer LS, Vesole DH, Greipp PR. Multicenter phase 2 trial of rituximab for Waldenström macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). *Leuk Lymphoma*. 2004;45(10):2047-2055.
58. Treon SP, Soumerai JD, Hunter ZR, et al. Long-term follow-up of symptomatic patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinemia treated with the anti-CD52 monoclonal antibody alemtuzumab. *Blood*. 2011;118(2):276-281.
59. Dimopoulos MA, Zomas A, Viniou NA, et al. Treatment of Waldenstrom's macroglobulinemia with thalidomide. *J Clin Oncol*. 2001;19(16):3596-3601.
60. Treon SP, Tripsas CK, Yang G, et al. A prospective multicenter study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenstrom's macroglobulinemia [ASH abstract 251]. *Blood.* 2013;122(21)(suppl).
61. Chen CI, Kouroukis CT, White D, et al; National Cancer Institute of Canada Clinical Trials Group. Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: a phase II study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(12):1570-1575.
62. Hellmann A, Lewandowski K, Zaucha JM, Bieniaszewska M, Hałaburda K, Robak T. Effect of a 2-hour infusion of 2-chlorodeoxyadenosine in the treatment of refractory or previously untreated Waldenström's macroglobulinemia. *Eur J Haematol*. 1999;63(1):35-41.
63. Porta C, Osanto S, Ravaud A, et al. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. *Eur J Cancer*. 2011;47(9):1287-1298.
64. Gertz MA, Reeder CB, Kyle RA, Ansell SM. Stem cell transplant for Waldenström macroglobulinemia: an underutilized technique. *Bone Marrow Transplant*. 2012;47(9):1147-1153.
65. Anagnostopoulos A, Hari PN, Perez WS, et al. Autologous or allogeneic stem cell transplantation in patients with Waldenstrom's macroglobulinemia. *Biol Blood Marrow Transplant.* 2006;12(8):845-854.
66. Treon SP, Hunter ZR, Matous J, et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248. *Clin Cancer Res.* 2007;13(11):3320-3325.
67. Liu ES, Burian C, Miller WE, Saven A. Bolus administration of cladribine in the treatment of Waldenström macroglobulinaemia. *Br J Haematol*. 1998;103(3):690-695.
68. Ghobrial IM, Roccaro A, Hong F, et al. Clinical and translational studies of a phase II trial of the novel oral Akt inhibitor perifosine in relapsed or relapsed/refractory Waldenstrom's macroglobulinemia. *Clin Cancer Res.* 2010;16(3):1033-1041.
69. Dreger P, Schmitz N. Autologous stem cell transplantation as part of first-line treatment of Waldenstrom's macroglobulinemia. *Biol Blood Marrow Transplant.* 2007;13(5):623-624.