

New developments in the management of Waldenström macroglobulinemia

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Abstract: Waldenström macroglobulinemia (WM) is a rare, immunoglobulin M -associated lymphoplasmacytic lymphoma. With the recent discoveries of *CXCR* warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) and *MYD88* mutations, our understanding of the biology of WM has expanded substantially. While WM still remains incurable, the field is rapidly evolving, and a number of promising agents with significant activity in this malignancy are being evaluated currently. In this review, we discuss the new developments that have occurred in WM over the past 15 years, with a focus on the role of ibrutinib, an oral Bruton's tyrosine kinase inhibitor that has recently been approved for WM in the United States, Europe, and Canada.

Keywords: lymphoplasmacytic lymphoma, indolent lymphoma, *MYD88*, *CXCR4*, management, ibrutinib

Introduction

The report of two patients by Waldenström¹ in the year 1944, presenting with epistaxis, hematemesis, lymphadenopathy, decreased fibrinogen level, increased blood viscosity, and elevated macroglobulins, was the first account of Waldenström macroglobulinemia (WM). WM is a rare, indolent lymphoma with lymphoplasmacytic infiltration of the bone marrow (BM) and monoclonal immunoglobulin M (IgM) gammopathy. The management of WM is evolving, with a deeper understanding of the disease pathophysiology and introduction of newer drugs. WM remains an incurable disease, with a median overall survival (OS) of ~8 years from diagnosis.^{2,3} In this review, we discuss new developments in the management of WM based on the data published over the past 15 years, with an emphasis on the role of Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, that has been recently approved for WM in the US, Canada, and European Union. To better serve our patients, a holistic understanding of this fascinating malignancy and its current and emerging therapeutic options remains paramount, and this review has been written with the intention of making our patients the ultimate beneficiaries.

Epidemiology

Approximately 1,500 new cases of WM are diagnosed in the US each year.⁴ The median age at diagnosis is ~70 years, with an incidence rate of 3.4 per million among men and 1.7 per million among women in the US.² Caucasians are predominantly affected.⁵

Although no proven inheritance patterns have been observed in WM to date, a population-based study was remarkable for demonstrating a 20-fold increased risk of development of lymphoplasmacytic lymphoma (LPL)/WM in the first-degree relatives

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of the patients.⁶ Moreover, the first-degree relatives were noted to have a three- to fivefold increased risk of developing another non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or monoclonal gammopathy of undetermined significance.⁶

Diagnosis

The Mayo Clinic criteria that must be met for the diagnosis of active WM are

1. serum IgM monoclonal protein of any size
2. BM lymphoplasmacytic infiltration of at least 10%.

Besides the BM, the lymphoplasmacytic cells can infiltrate extramedullary sites, predominantly the lymph nodes and the spleen, with a spectrum of clonal B cells, including small lymphocytes, plasmacytoid lymphocytes (showing features of both plasma cells and lymphocytes), and plasma cells. In contrast to the Mayo Clinic criteria, the International Workshop on Waldenström's Macroglobulinemia (IWWM) Consensus criteria merely require the presence of a lymphoplasmacytic infiltrate in the marrow and serum IgM monoclonal protein of any size to establish a diagnosis of WM. The typical immunophenotypic signature of the infiltrate is surface IgM⁺, CD5[±], CD10⁻, CD19⁺, CD20⁺, CD22⁺, CD23⁻, CD25⁺, CD27⁺, FMC7⁺, CD103⁻, and CD138⁺.^{7,8}

Pathogenesis

Although the exact etiology of WM remains unclear to date, the whole genome sequencing (WGS) has identified important mutations that appear to be pathogenic. Recent studies have partially unraveled the role of myeloid differentiation factor 88 (*MYD88*) mutations in the pathogenesis of WM. The *MYD88* protein is involved in the signal transduction pathways activating nuclear factor kappa B (NFκβ) and mitogen-activated protein kinase (MAPK).⁹ Its activation is enhanced by the mutations occurring in the *MYD88* gene, which induce tumorigenesis.⁹ The WGS in WM has identified a somatic variant (T → C) at position 38182641 in chromosome 3p22.2 that harbors the *MYD88* gene.¹⁰ The *MYD88*^{L265P} mutation leads to an amino-acid change from leucine to proline (L265P) in the *MYD88* protein.¹⁰ The protein is capable of hyperactivating NFκβ via interleukin-1 receptor-associated kinase (IRAK) and BTK pathways through phosphorylation, thereby increasing cell survival.¹¹ Treon et al¹⁰ reported that *MYD88*^{L265P} is a common mutation in WM with a prevalence of 91%. Patients with *MYD88*^{L265P} mutation are noted to have distinct disease profile, including higher serum IgM levels, hyperviscosity, and higher BM involvement compared to their counterparts harboring the *MYD88* wild-type gene.¹²

Another seminal discovery is that of the somatic mutations involving the C-X-C chemokine receptor type 4 (*CXCR4*, also known as Fusin or CD184), encoded by the *CXCR4* gene.^{13,14} The association in WM bears a striking similarity to the finding observed in the warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome that also results from a mutation in the *CXCR4* gene.^{12,15} The *CXCR4* mutations have been observed in 27–40% of patients with WM and were found to be involved with its pathogenesis.^{12,15,16} These mutations lead to the formation of a truncated receptor protein associated with a high expression of *CXCR4* receptor and could be either nonsense (*CXCR4*^{WHIM/NS}) type or frameshift (*CXCR4*^{WHIM/FS}) type.

Genotypic–phenotypic association

A single retrospective study by the Dana–Farber Cancer Institute¹² noted that the *MYD88*^{L265P} with *CXCR4*^{WHIM/NS} genotype was associated with severe disease, greater BM involvement, and increased likelihood of developing hyperviscosity-related complications with higher serum IgM levels.

The patients with *MYD88*^{L265P} and *CXCR4*^{WHIM/FS} genotypes also exhibit an aggressive disease course. However, the disease severity of patients with *MYD88*^{L265P} and *CXCR4*^{WHIM/FS} genotypes appears milder compared to their *MYD88*^{L265P} and *CXCR4*^{WHIM/NS} counterparts (Table 1).^{12,15} The patients with *MYD88*^{WT}*CXCR4*^{WT} show the lowest marrow involvement.¹² Despite the association of severe disease with *MYD88*^{L265P} and *CXCR4*^{WHIM/NS} or *FS* mutations compared to *MYD88*^{WT}*CXCR4*^{WT}, the survival outcomes do not appear to be affected by the presence of *CXCR4* mutations. Rather, the outcomes appear to be impacted by the *MYD88* mutation status and were found to be surprisingly better for the patients harboring *MYD88*^{L265P} gene than the patients harboring *MYD88*^{WT} gene in one study.¹² Importantly, we now know that the presence of *MYD88* and *CXCR4* mutations will affect the degree of response to ibrutinib (discussed in the subsequent section). Another recent article on the transcriptional profiling (RNAseq) and comparison of the WM patients to the normal population without B-cell disorders attempted to shed more light on this matter. Four genotypic groups as indicated in Table 1 are currently identifiable.^{16,17}

Clinical presentation

The clinical presentation and the disease characteristics of WM could be attributed to tumor/B-lymphocyte infiltration or monoclonal immunoglobulins as summarized in Table 2.

Presentation of WM could be heterogenous. Some of the most common presenting features are hyperviscosity,

Table 1 Genotypic–phenotypic association in WM

Clinical Characteristics	MYD88 ^{L265P} CXCR4 ^{WT}	MYD88 ^{L265P} CXCR4 ^{WHIM/FS}	MYD88 ^{L265P} CXCR4 ^{WHIM/NS}	MYD88 ^{WT} CXCR4 ^{WT}
IgM	↑↑	↑↑	↑↑↑↑	↑
BM infiltration	↑↑↑	↑↑	↑↑↑↑	↑
Sensitivity to BTK inhibitors	↑↑↑	↑↑	↑	↓
Incidence (%)	~60	27–40*	27–40*	<10

Notes: This table is a relative semiquantitative representation of the frequency of disease characteristics with various genetic mutations. *Frameshift (FS) and nonsense (NS) mutations are almost equally divided among WM patients with CXCR4 somatic mutations.

Abbreviations: BM, bone marrow; BTK, Bruton's tyrosine kinase; IgM, immunoglobulin M; WM, Waldenström macroglobulinemia.

Table 2 Disease characteristics of WM

Parameter	Clinical characteristics
Features attributable to tumor infiltration	Constitutional symptoms: recurrent fever, night sweats, weight loss, and fatigue Cytopenias due to BM infiltration Organomegaly Lymphadenopathy
Features attributable to monoclonal immunoglobulin	Hyperviscosity that may present as oro-nasal bleeding, blurred vision, headache, dizziness, vertigo, ataxia, peripheral neuropathy, altered sensorium, and encephalopathy ⁸⁷ Deposition of IgM as amorphous material in heart, kidney, and gastrointestinal tract causing amyloidosis or IgM infiltrative disease Coombs' positive autoimmune cold hemolytic anemia and cryoglobulinemia ^{88,89} Neuropathy due to IgM directed against myelin-associated glycoprotein or other neural components ⁹⁰

Abbreviations: BM, bone marrow; IgM, immunoglobulin M; WM, Waldenström macroglobulinemia.

constitutional symptoms, bleeding, and neurologic symptoms.^{18,19} Lymphadenopathy, hepatomegaly, splenomegaly, and fundoscopic abnormalities may be detected.^{18,19} Anemia is a common presenting feature, and type I cryoglobulinemia may be infrequently encountered.^{18,19}

Prognosis and natural history

A large study involving >5,000 patients with WM from 1991 to 2010 showed that the median OS for the entire cohort was 7 years and the 5- and 10-year OS were 62% and 39%, respectively.² The 5-year OS for patients who were diagnosed prior to the age of 70 years compared to those older than 70 years was 71% and 39%, respectively.⁴ The OS has increased over the last two decades; the median OS for the patients diagnosed between 1991 and 2000 was 6 vs 8.2 years for those diagnosed between 2001 and 2010, $P < 0.05$.^{2,20}

Smoldering WM

At the time of diagnosis, ~25% of patients with WM do not have symptoms or signs that are attributable to an increased monoclonal protein or infiltration by malignant cells. This population of patients is considered to have smoldering WM, and there are no indications for the initiation of treatment until the development of symptoms or significant anemia/thrombocytopenia in this patient population given the risks involved and the lack of survival advantage with early treatment.²¹ The OS rate of patients with smoldering WM can approximate that of the normal age-matched population.⁸ A Mayo Clinic

study demonstrated that the rate of progression of patients with smoldering WM to symptomatic WM during a 15-year follow-up was 71%, and the cumulative risk of progression of smoldering WM to symptomatic WM, amyloidosis, or a related disorder was 6% at 1 year, 39% at 3 years, 59% at 5 years, and 68% at 10 years.²²

Prognosis

The International Prognostic Symptom Score (IPSS) for WM was created to assess the disease prognosis and survival risk in patients with active WM who require treatment (Table 3).²³

Treatment

The optimal initial approach requires assessment of the symptomatology, the genetic signature, ie, *MYD88* status (*CXCR4* status is not routinely used in practice at present), the monoclonal protein size, age of the patient, and certain laboratory parameters. The decision to commence therapy typically should not be based on the size of serum IgM size.²⁴ The treatment indications for symptomatic patients are outlined in Table 4.^{21,24,25}

Furthermore, the therapy-related decisions depend on the rapidity with which the symptom control is necessary. Hyperviscosity-related symptoms warrant urgent plasmapheresis.^{25,26} Other indications that require immediate reduction in IgM protein include moderate-to-severe hemolytic anemia, bulky lymphadenopathy, and symptomatic cryoglobulinemia.

Table 3 Disease prognosis based on IPSS

Prognostic factors	Cutoffs at which the factor is considered adverse at the time of initiation of treatment	
Age	≥65 years	
Hemoglobin	≤11.5 g/dL	
Platelets	≤100×10 ⁹ /L	
β2-Microglobulin	>3 mg/L	
Serum monoclonal IgM	>7 g/dL	
Risk stratification	Criteria	5-Year survival (%)
Low	≤1 adverse variable (except age)	87
Intermediate	2 adverse variables or age >65 years	68
High	>2 adverse variables	36

Abbreviations: IgM, immunoglobulin M; IPSS, International Prognostic Symptom Score.

Table 4 Treatment indications for symptomatic patients

Clinical indications	Laboratory indications
Signs and symptoms associated with hyperviscosity	Hemoglobin <10 g/dL
Moderate to severe peripheral neuropathy	Platelet count <100×10 ⁹ /dL
AL amyloidosis	Hemolytic anemia
Symptomatic cryoglobulinemia	
Constitutional symptoms, Raynaud's phenomenon, and arthralgia	
Bulky or symptomatic lymphadenopathy	
Symptomatic organomegaly	

Abbreviation: AL, amyloid light-chain.

Immunotherapy

Rituximab, a chimeric anti-CD20 monoclonal antibody, serves as a backbone of therapy directed against CD20⁺ WM cells.^{27–29} The two important side effects include IgM flare and late-onset neutropenia (LON). IgM flare (defined as a transient increase in IgM levels by at least 25% from the baseline pretreatment levels) is generally seen in patients with serum IgM levels >4 g/dL. It is typically encountered in the first month of rituximab therapy but at times can persist for several months.³⁰ In patients with hyperviscosity symptoms and IgM >4 g/dL, preemptive plasmapheresis and avoidance of rituximab during the first 1–2 cycles is recommended.^{31,32} LON is a poorly understood complication of rituximab with a speculated correlation to FcγRIIIa-V158*F polymorphism secondary to profound antibody-dependent cell-mediated cytotoxicity activity and pronounced B-cell depletion associated with this polymorphism, causing neutrophil destruction by the release of granzyme and lysozyme.^{33–36} Ofatumumab, a fully human anti-CD20 antibody, targets an epitope that is different from that of rituximab. It may be used in patients who are intolerant of rituximab, but higher cost and the lack of data suggesting superiority over rituximab restrict its use.^{37,38}

Chemoimmunotherapy

Alkylator-based combination therapy has been considered highly effective in WM. Dexamethasone and rituximab in combination with cyclophosphamide (DRC) is a commonly prescribed regimen. Adriamycin and vincristine are avoided in WM owing to significant side effects without substantial additional benefit.³⁹ The DRC regimen is unsuitable for rapid control of symptoms as the median time to response is 4.1 months.⁴⁰ The 8-year OS rates in IPSS for WM low-, intermediate- and high-risk patients have been reported to be 100%, 55%, and 27%, respectively. The median progression-free survival (PFS) with DRC is 35 months (95% CI: 22–48 months). Patients who relapse after DRC are found to be still sensitive to rituximab. The regimen appears to be safe in both short and long terms.^{40,41}

A subset analysis of a Phase III, open-label trial by Rummel et al, comparing bendamustine in combination with rituximab (BR) with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), showed a markedly improved median PFS with BR (69.5 [36.6–73] months vs 28.1 [17.8–51] months with R-CHOP). Both regimens led to an overall response rate (ORR) that approximated 95%. The patients who received BR tolerated therapy better, with lower rates of high-grade neutropenia, infectious complications, peripheral neuropathy, and absence of alopecia.⁴² Of note, patients with severe functional defects of the organ dysfunction (NYHA III or IV, creatinine >2 mg/dL, aspartate aminotransferase/alanine aminotransferase/bilirubin >3× upper limit of normal) were excluded.⁴² Due to the superior tolerability of BR, the Mayo Clinic group suggests using BR as the front-line option in patients with symptomatic WM.⁷ Comparable results, with an ORR of 80% and 83%, were reported in two retrospective studies involving relapsed/refractory WM patients treated with BR.^{43,44} Prolonged cytopenias are frequent in patients receiving BR who have previously received nucleoside analog therapy.⁴⁴ Truncation of BR therapy from six to four cycles

to avoid the prolonged cytopenias is not uncommon owing to comparable efficacy.⁴⁵ Reduction of the dose from 90 to 60–70 mg/m² in the elderly and those with compromised renal function is also a common practice.³⁹

A survival benefit with nucleoside analog in WM was demonstrated in a multicenter Phase III randomized WM1 trial (trial comparing chlorambucil with fludarabine in patients with advanced WM). Oral fludarabine in comparison to chlorambucil resulted in a significantly longer PFS (36 vs 27 months; $P=0.012$) and OS (not reached vs 70 months; $P=0.014$), with a longer duration of response (38 vs 20 months; $P<0.001$).⁴⁶ In this study, myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) developed in ~1.5% in the chlorambucil arm, but surprisingly, this complication was not observed in the fludarabine-treated patients.⁴⁶ Despite being highly effective, nucleoside analogs are less preferred now in the frontline setting owing to the risk of second malignancies.^{39,47} Because nucleoside analogs can also adversely impact stem-cell mobilization, they are best avoided as frontline therapies in the transplant-eligible patients. We typically reserve the use of nucleoside analogs for the relapsed–refractory population.

The proteasome inhibitors are among the most effective therapies in WM, particularly when combined with a steroid and rituximab.^{48,49} In the initial trial by the Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG) using this combination in 23 treatment-naïve WM patients, the ORR was 96%, with a median time to response of 1.4 months. The rapid response prompted physicians to use this combination in patients with hyperviscosity syndromes.⁵⁰ Strikingly, despite substantial response, 60% of patients discontinued therapy after four cycles due to severe neuropathy. Investigators have attempted to reduce the incidence of treatment-emergent neuropathy by switching to weekly administration (three doses per cycle, D_{1,8,15}) or using subcutaneous doses (NCT01788020). Preliminary data show that subcutaneous bortezomib in combination with rituximab and cyclophosphamide is quite effective.⁵¹ Bortezomib-based therapy may be considered in patients with severe symptoms requiring rapid decrease in the monoclonal protein. Bortezomib is nonmyelotoxic and, therefore, can potentially be also used for maintenance therapy in patients without neuropathy, although clinicians should be vigilant about treatment-emergent neuropathy. An antiviral prophylaxis is required for the prevention of herpes zoster. A novel combination of carfilzomib, rituximab, and dexamethasone (CaRD) used as a neuropathy-sparing regimen in patients with WM led to 87% ORR and 36% VGPR when used as frontline therapy.⁵² Other novel proteasome inhibitors that are being investigated

include oprozomib (an oral epoxyketone irreversible proteasome inhibitor) and ixazomib (an oral boronic acid-based reversible proteasome inhibitor).^{39,53–55}

Immunomodulatory drugs (IMiDs)

The use of IMiDs has been attempted in WM, given their impressive activity in MM. Thalidomide has been shown to be quite effective in WM.^{56–59} Coleman et al⁵⁷ reported its use in patients previously treated with a purine analog or alkylating agent in combination with clarithromycin and dexamethasone. This combination was suggested as a salvage regimen in heavily pretreated patients.⁵⁹ Thalidomide in combination with rituximab led to an ORR of 72%.⁵⁸ The major disadvantage was the high incidence of neurotoxicity and poor tolerability by elderly patients.^{56–59} Lenalidomide has been evaluated in Phase I and II trials in the setting of WM. Due to the dose limiting toxicity at 20 mg, a dose of 15 mg was used for 21 of 28 days. At a median follow-up of 36 months, the time to progression (TTP) was 16 months and the 5-year OS was 91%. Combination of lenalidomide and rituximab led to abrupt decrease in hemoglobin in 88% of the patients.⁶⁰ Investigators also evaluated the combination of pomalidomide with dexamethasone and rituximab (NCT01078974) in a dose-escalating Phase I study in seven patients, with a median time to response of 2.1 months and a median response duration of 15 months. A substantial proportion of patients (3/7) required plasmapheresis for IgM flare due to which the study was prematurely terminated. Given these issues, IMiDs have not been considered particularly attractive in WM.

Other agents

Everolimus, an inhibitor of mechanistic (formerly mammalian) target of rapamycin (mTOR) was studied in 60 relapsed/refractory patients with WM. The median time to remission was 2 months with a median PFS of 4 months. Major remission and partial remission were noted in 23% and 50% of the patients, respectively, with 23% developing grade 3/4 cytopenias.⁶¹ The use of everolimus was also attempted in treatment-naïve patients of WM with an ORR of 66.7% and major responses of 42.4%.⁶² Severe adverse events included significant cytopenias, oral ulceration (prevented by dexamethasone swashes), and pulmonary toxicity. Everolimus has been tried in combination with bortezomib and rituximab (RVR), demonstrating a median PFS of 21 months.⁶³

Idelalisib targets the PI3K pathway, which is activated in patient with *MYD88* mutation. de Rooij et al described the inhibition of WM cells' proliferation by idelalisib. They also suggested that both idelalisib and ibrutinib dislodge the

WM cells from the microenvironment into the circulation, which leads to the death of these cells in the absence of a supportive niche.⁶⁴ Recently, a Phase II study evaluating the safety and efficacy of idelalisib in patients with relapsed and/or refractory symptomatic WM was prematurely closed owing to the high incidence of hepatotoxicity.⁶⁵ Sildenafil, a phosphodiesterase inhibitor, was serendipitously found to be effective after an unusual response in the disease status of five WM patients following the prescription of sildenafil for erectile dysfunction.⁶⁶ Table 5 summarizes the dosing schedules and outcomes of rituximab treatment as monotherapy and as combination therapy when combined with various abovementioned treatment regimens.

Role of ibrutinib in the management of WM

Ibrutinib, an oral BTK inhibitor, acts by inhibiting downstream signaling of B-cell receptor pathway. By impairing crosstalk between *MYD88* and BTK, it induces apoptosis of WM cells.⁶⁷ Additionally, it has a role in inhibiting hematopoietic cell kinase (HCK) as described below in detail.

The important pharmacological aspects of ibrutinib and the various clinical trials conducted to date to evaluate its role in WM are tabulated in Tables 6 and 7, respectively.

Ibrutinib as monotherapy

The first Phase II multicenter clinical trial to show the efficacy of ibrutinib in relapsed–refractory WM (≥ 1 prior therapy) was NCT01614821 that led to this agent's approval in WM in the US, Europe, and Canada. The population studied had received a median of two lines of therapy (range: 1–9 lines), with a median BM involvement of 60% (3–95%). IgM decreased rapidly as suggested by a median time to partial response of 8 weeks and the achievement of minimal responses as early as 4 weeks from the start of therapy.⁶⁸ The best clinical responses to ibrutinib at a median duration of treatment of 19 months (0.5–29.7 months) were an ORR of 91% and a major response rate of 73%. Complete response (CR) with ibrutinib monotherapy was strikingly absent. The short follow-up showed a 2-year PFS and an OS of 69.1% and 95.2%, respectively.⁶⁸ Ibrutinib monotherapy has also been evaluated as a part of the iNNOVATE™ study in patients refractory to rituximab.

Table 5 Various regimens with rituximab in WM

Regimen	Schedule	Responses	TTP/PFS
Rituximab monotherapy – standard dosing ^{27–29}	375 mg/m ² × 4 weekly doses	ORR: 30–60%; VGPR/CR: 0–5%	DOR: 8–11 months
Rituximab monotherapy – extended schedule ^{27–29}	375 mg/m ² × 4 weekly doses (weeks 1–4) + repeat 4 weekly doses (weeks 12–16)	ORR: 35–45%; VGPR/CR: 5–10%	DOR: 16–29 months
Ofatumumab monotherapy ³⁸	300 mg for weeks 1 to 2–4 with either standard dose: 1 g/week or high dose: 2 g/week in patients with minor response/stable disease – week 16: 300 mg → 2 g/week × 4 weeks (weeks 17–20)	ORR: 59%; major response: 35%	
Rituximab + alkylator (DRC) ⁴⁰	Dexamethasone 20 mg IV → rituximab 375 mg/m ² IV on D ₁ and cyclophosphamide 100 mg/m ² orally bid on D _{1–5} (total dose, 1,000 mg/m ²) every 21 days × 6 cycles	ORR: 83%; major response: 74%	Median PFS: 35 months
Rituximab + alkylator (bendamustine) ⁴²	90 mg/m ² bendamustine D ₁ /D ₂ ; 375 mg/m ² rituximab on D ₁ repeated every 4 weeks × 6 cycles	ORR: 95%	PFS: 69.5 months
Rituximab + proteasome inhibitor (bortezomib – BDR) ⁵⁰	Bortezomib – 1.3 mg/m ² IV – D _{1,4,8,11} ; dexamethasone – 40 mg IV – D _{1,4,8,11} ; rituximab – 375 mg/m ² IV – D ₁₁ every 21 days × 4 cycles of induction and 4 cycles from 3 months as maintenance	ORR: 96%; major responses: 83%	Median PFS: 66 months
Rituximab + proteasome inhibitor (carfilzomib – CaRD) ⁵²	Carfilzomib (20 mg/m ² – cycle: 1, 36 mg/m ² – cycles: 2–6); rituximab (375 mg/m ² , D _{2,9}); dexamethasone (20 mg, D _{1,2,8,9}) every 21 days × 6 cycles	CR: 87%; VGPR: 36%	Median PFS: >16 months
Rituximab + IMiD ⁶⁰	Rituximab (375 mg/m ² , weekly on weeks 2–5 and 13–16) and len 25 mg for 21/28 days	ORR: 50% (abrupt decrease in Hgb in 88% of patients)	Median TTP: 17.1 months
Rituximab + mTOR inhibitor + bortezomib ⁶³	Everolimus – 10 mg PO daily; bortezomib 1.6 mg/m ² IV D _{1,8,15} for 28 days/cycle × six cycles; rituximab 375 mg/m ² IV D _{1,8,15,22} – cycles 1 and 4 only	ORR: 89%	Median PFS: 21 months

Abbreviations: BDR, bortezomib dexamethasone rituximab; CaRD, carfilzomib, rituximab and dexamethasone; CR, complete response; D, dexamethasone; DOR, duration of response; DRC, dexamethasone and rituximab in combination with cyclophosphamide; Hgb, hemoglobin; IMiD, immunomodulatory drug; IV, intravenous; Len, lenalidomide; mTOR, mechanistic target of rapamycin; ORR, overall response rate; PFS, progression-free survival; PO, oral; TTP, time to progression; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Table 6 Aide memoirs on ibrutinib

Pharmacokinetics	Dose modifications	Interactions
<ul style="list-style-type: none"> • A BTK inhibitor • $t_{1/2}$ – 2–3 h • Oral bioavailability – good • Peak plasma levels – 1–2 h • Clearance – liver metabolism by CYP3A • Elimination $t_{1/2}$ – 4–6 h 	<ul style="list-style-type: none"> • Renal modification <ul style="list-style-type: none"> • No modification required • Monitor toxicities • Hepatic modification based on Child–Pugh classification <ul style="list-style-type: none"> • Class A – ↓ to once daily • Classes B and C – avoid usage 	<ul style="list-style-type: none"> • CYP3A inducers – ↓ plasma level • Antiepileptics: carbamazepine and phenytoin • Antitubercular: rifampin • St John's wort • CYP3A inhibitors – ↑ plasma level <ul style="list-style-type: none"> • Antivirals (protease inhibitors) • Antifungals (azoles) • Macrolides • Food interactions: avoid <ul style="list-style-type: none"> • Seville orange • Starfruit • Grapefruit juice
Special category of population	Dosage	Side effects
<ul style="list-style-type: none"> • Pregnancy – avoid pregnancy for 1 month after cessation of therapy • Males – avoid fathering for 1 month after cessation of therapy • Breast feeding – not studied; decision based on the risk–benefit ratio for the mother's health vis-à-vis exposure to newborn • Surgery – withhold 3–7 days before and after surgery depending on the bleeding risk involved with the surgery 	<ul style="list-style-type: none"> • Capsule strength – 140 mg • Dose – three tablets per day • Timing with regard to food intake – no bearing on the bioavailability • Missed dosing – to take capsule as soon as the patient remembers in the same day; no additional dosing on subsequent day recommended for missed doses 	<ul style="list-style-type: none"> • Bleeding <ul style="list-style-type: none"> • Platelet dysfunction • Aggravation of avWD secondary • Atrial fibrillation, hyper/hypotension • Headache and dizziness • Cytopenias • Infections • Gastrointestinal disturbances • Fatigue, musculoskeletal pain, and arthralgias

Abbreviations: avWD, acquired von Willebrand's disease; BTK, Bruton's tyrosine kinase.

Table 7 Studies using ibrutinib monotherapy in WM

Reference	Type of study	Sample size	Disease setting	Outcome
Advani et al ⁹¹	Phase I	4 ^a	RR	75% achieved response and continued to have response at 4 years ⁹²
Treon et al ⁶⁸	Phase II	63	RR	ORR – 95% OS – 95% at 2 years PFS – 69% at 2 years
Dimopoulos et al, ⁶⁹ iNNOVATE™	Phase III	31	Refractory to last rituximab containing therapy	ORR – 90% OS – 92% at 18 months PFS – 86% at 18 months

Note: ^aOut of total 56 patients of CLL/NHL.

Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR, relapsed and/or refractory; WM, Waldenström macroglobulinemia.

The therapy was effective with a high ORR of 90% and an estimated 18-month OS of 97% and PFS of 86% (Table 7). The median time to best response was 2 months.⁶⁹ Adverse events included grade 1–2 thrombocytopenia (13%) and diarrhea (36%) and grade 3 neutropenia (10%) and hypertension (10%). A vast majority of serious adverse events were related to infections.⁶⁹

Effect of mutations on the efficacy of ibrutinib

CXCR4 mutations confer resistance to ibrutinib. In vitro studies of the *CXCR4*^{WHIM}-engineered WM cells demonstrated that the presence of a mutation in the *CXCR4* gene

of the cells decreases their apoptosis following CXCL12 stimulation owing to the persistent activation of AKT and extracellular signal-regulated kinases.⁷⁰ These survival effects of *CXCR4*^{WHIM} mutation are abrogated by the inhibition of simultaneous *MYD88*^{L265P} signaling.⁷¹ Treon et al⁷² have demonstrated significant differences in response rates (ORR and major response rate) in patients with *MYD88*^{L265P}/*CXCR4*^{WT}, *MYD88*^{L265P}/*CXCR4*^{WHIM}, and *MYD88*^{WT} mutations; the major response rate was 62% in patients with mutated *MYD88* and *CXCR4*^{WHIM} gene and 92% in those with mutated *MYD88* and *CXCR4*^{WT} gene, whereas no major response was observed in patients with *MYD88*^{WT}/*CXCR4*^{WT} genotype. Of the arm C study population (n=31) of the iNNOVATE trial, 25 patients

underwent mutation analysis, of which *MYD88*^{L265P}/*CXCR4*^{WT} mutation status and *MYD88*^{L265P}/*CXCR4*^{WHIM} mutation status were seen in 17 and 7 patients, respectively.⁶⁹ Though this study was not powered to assess the differences of treatment response with respect to mutation status, major response was seen in 82% of patients with *MYD88*^{L265P}/*CXCR4*^{WT} genotype and 71% of patients with *MYD88*^{L265P}/*CXCR4*^{WHIM} genotype.⁶⁹ IgM reduction was greater and achieved earlier in patients with *MYD88*^{L265P}/*CXCR4*^{WT} mutation status than in patients with *MYD88*^{L265P}/*CXCR4*^{WHIM} mutation status.⁶⁹ Therefore, for ibrutinib-treated patients with WM, the *MYD88*^{L265P} mutation serves as a favorable prognostic marker, while the *CXCR4* mutation is a predictive marker, and it is reasonable to check for the presence of *MYD88*^{L265P} mutation prior to subjecting a patient to indefinite ibrutinib therapy, ie, until progression or intolerable side effects.⁷

Adverse effects of ibrutinib

Adverse events include cytopenias, infections, arrhythmias, and bleeding (particularly epistaxis). Previously treated patients with WM were more likely to experience cytopenias with ibrutinib.

A tenfold increase in the risk of atrial fibrillation (AFib) in the ibrutinib arm was first noticed in the randomized Phase III open-label RESONATE study comparing ibrutinib and ofatumumab in 391 refractory CLL/SLL patients.⁷³ A meta-analysis to evaluate the risk of AFib in patients on ibrutinib vs the comparator drug/arm in random and fixed effects models showed a relative risk of 3.5 and 3.9, respectively. The rate of AFib on pooled analysis of the 20 studies was 3.3 per 100 person years.⁷⁴ Gustine et al⁷⁵ reported the cumulative risk of AFib of 5.4, 7.1, and 8.9% in 112 WM patients on ibrutinib at 1, 2, and 3 years, respectively. A past history of AFib leads to a shorter recurrence time of 3.9 vs 33.4 months in otherwise asymptomatic patients, and dose reduction and cardiologic intervention allowed the patients to continue therapy.⁷⁵ Ibrutinib should be avoided in patients with AFib on anticoagulation.²⁵ Animal experiments have suggested a role of ibrutinib in the inhibition of the cardiac PI3K–AKT signaling as the cause of the development of AFib.⁷⁶ Although a decrease in QTc interval is another potential cardiac side effect with ibrutinib, its significance is unclear. Ibrutinib also leads to platelet aggregation abnormalities and is best avoided in patients concurrently on other antiplatelet agents that have a potential to cause bleeding diathesis/platelet dysfunction.⁷⁷ This off-target effect was first observed in CLL trials. Acquired von Willebrand's disease (aVWD) can be infrequently encountered in WM patients (~5%) due to

elevated IgM levels.⁷⁸ Therefore, it is reasonable to check aVWD levels/activity prior to commencing ibrutinib in WM patients with a history of bleeding.²⁵

Experimental combinations of ibrutinib with novel agents

The aforementioned multicenter study (iNNOVATE; NCT02165397) began enrollment in July 2014 in 51 centers across the world to study the role of ibrutinib in combination with rituximab. This is primarily a randomized controlled trial wherein patients receive rituximab (4 weekly doses of 375 mg/m² IV, with repeat 4 weekly doses after 3 months), with or without ibrutinib 420 mg daily until progression or unacceptable toxicity. WM patients who are treatment naive as well as those with documented progression and no response to their most recent treatment regimen were included in the study. Those patients who were refractory to rituximab-containing regimen were excluded from randomization but studied separately in an open-label arm with single-agent ibrutinib, the results of which were discussed earlier (Table 7).

IRAK1 is another protein downstream of BTK, which can contribute to the WM cell survival after exposure to ibrutinib. WM cells with *MYD88* mutation show preferential IRAK1 rather than IRAK4 signaling. A combination therapy of ibrutinib with IRAK inhibitors can potentially augment the NFκβ blockade and theoretically overcome ibrutinib resistance.⁷⁹

Yang et al have demonstrated the overexpression of hemopoietic cell kinase (HCK) in WM cell lines with *MYD88*^{L265P} mutation based on transcriptome profiling. The efficacy of ibrutinib in WM cell lines with *MYD88*^{L265P} mutation was directly correlated to its binding to HCK, whereas mutated HCK blocked ibrutinib-related tumor cell killing. This study implicated the HCK pathway for ibrutinib resistance and a novel target in patients with *MYD88* mutation.^{80,81}

B-cell CLL/lymphoma 2 (BCL2) antagonist, venetoclax, is effective in WM with *CXCR4*^{WHIM} mutation that is known to cause resistance to BTK and PI3K inhibitors. A study on the cell lines derived from WM patients with *CXCR4*^{WHIM} mutations showed enhanced apoptosis with ibrutinib and idelalisib in the presence of venetoclax. Activity of venetoclax as a single agent has also been demonstrated in cell lines with *CXCR4*^{WT} mutations and is postulated to be due to overexpression of BCL2 by the WM cells.⁸² Aurora kinase inhibitors have also been proposed for therapy in patients exhibiting ibrutinib resistance.⁸³

Role of stem cell transplant in WM

Autologous stem cell transplant (ASCT) is a therapeutic consideration for the young patients with relapsed disease. Patients who are considered eligible for transplantation should avoid induction with drugs that are stem cell toxic.^{7,39} The European Bone Marrow Transplant Registry (EBMTR) data on 158 patients who underwent ASCT for WM suggest a 5-year OS of 69% and a PFS of 49%, with nonrelapse mortality (NRM) of 5.6%.⁸⁶ Patients undergoing transplant in the first remission had a significantly superior outcome as compared to those undergoing ASCT at a later time (5-year disease-free survival [DFS] of 50% vs 40%; $P=0.004$, and 5-year OS of 71% vs 63%; $P=0.033$).^{84,85}

Allogeneic hematopoietic stem cell transplant (allo-SCT) has a very limited role, given the high transplant-related mortality, and we do not recommend this approach outside of clinical trials. Some experts suggest restricting its use primarily to young patients with multiple relapsed–refractory disease and particularly to those with early relapse post-ASCT. The reported ORR was 76%, the 5-year PFS was 56%, and the OS was 62% in a cohort of 86 patients. Twenty percent of patients achieved CR with allo-SCT. The 3-year NRM was 33% in patients receiving full myeloablative conditioning and 23% in patients receiving reduced-intensity conditioning.⁸⁶

Conclusion

With the introduction of molecular prognostic markers and improved understanding of the role of *MYD88* and *CXCR4* mutations in the pathophysiology of WM, the field appears to be rapidly evolving. The efficacy of multiple new agents including the second-generation BTK inhibitor (acalabrutinib), *BCL2* inhibitors, *IRAK* inhibitors, and monoclonal antibodies, such as belimumab (anti-Blys) and ulocuplumab (anti-*CXCR4*), is being evaluated. Given the remarkable strides that have been made recently in our understanding of this rare malignancy, we suspect that the treatment options are bound to improve in the coming years, albeit at the cost of making its management increasingly complex.

Disclosure

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