Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2013 September ; 13(0 2): . doi:10.1016/j.clml.2013.05.023.

Novel Treatment Options for Waldenström's Macroglobulinemia

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Abstract

Waldenström's macroglobulinemia first described by Jan Waldenström in 1944 is a lymphoplasmacytic lymphoma characterized by the presence of an immunoglobulin M (IgM) monoclonal gammopathy in the blood and monoclonal small lymphocytes and lymphoplasmacytoid cells in the bone marrow. WM is a rare and indolent disease but remains incurable. In this review we discuss the pathogenesis of Waldenström macroglobulinemia and focus on novel treatment options that target pathways deregulated in this disease. Recent studies have helped us identify specific genetic mutations that are commonly seen in WM and may prove to be important therapeutic targets in the future. We discuss the role of epigenetics and the changes in the bone marrow microenvironment that are important in the pathogenesis of WM. The commonly used drugs are discussed with a focus on novel agents that are currently being used as single agents or in combinations to treat WM. We finally focus on some agents that have shown preclinical efficacy and may be available in the near future.

Introduction

Waldenström's macroglobulinemia (WM) was first described by Jan Waldenström in 1944 when he identified two patients with oronasal bleeding, cytopenias, and a bone marrow showing predominantly lymphoid cells. WM is classified as a lymphoplasmacytic lymphoma according to the Revised European American Lymphoma and World Health Organization. WM is an incurable low-grade B-cell lymphoproliferative disorder characterized by the presence of an immunoglobulin M (IgM) monoclonal gammopathy in the blood and monoclonal small lymphocytes and lymphoplasmacytoid cells in the bone marrow [1-3]. WM is a rare disease with 1500 new cases diagnosed per year in the USA [4]. The main risk factor for the development of Waldenström macroglobulinemia is the presence of IgM-monoclonal gammopathy of undetermined significance, which confers a 46-fold higher relative risk to develop WM than the general population. In addition, about 20% of patients with Waldenström macroglobulinemia have at least one first degree relative with a B-cell neoplasm [5]. The clinical manifestations of WM include anemia and other cytopenias, hyperviscosity symptoms, deposition in tissues including amyloidosis, and other related disorders including peripheral neuropathy, hemolytic anemia, and cryoglobulinemia. Other rare manifestations include Schnitzler's syndrome, infiltration of organs such as the central nervous system (Bing-Neel syndrome), lung infiltrates, and lytic bone lesion. The

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median overall survival of patients with WM is 5–10 years. Patients with asymptomatic disease should not be treated based on monoclonal protein level alone [2, 6, 7].

In this review, we discuss the pathogenesis of Waldenström macroglobulinemia. We then focus on novel treatment options that target pathways deregulated in this disease.

Pathogenesis of Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia is defined as a lymphoplasmacytic lymphoma with bone marrow involvement and an IgM monoclonal gammopathy [8]. In addition to characteristic bone marrow infiltration, some adenopathy and extranodal involvement are common. About 15-20% of patients with WM also have splenomegaly, hepatomegaly and/or adenopathy [9].

Morphologically, bone marrow in WM is characterized by nodular, diffuse and/or interstitial infiltrate usually composed predominantly of small lymphocytes admixed with variable number of plasma cells and plasmacytoid lymphocytes [10]. The cells express B-cell associated antigens (CD19, CD20, CD79a) and also surface Ig. The plasmacytic cells express cytoplasmic Ig, usually IgM. An increased number of mast cells are noted close to the lymphoid aggregates. Dutcher bodies (PAS+ intranuclear pseudoinclusions) are present in the plasma cells. Lymph nodes that are involved with WM commonly show retention of the normal architecture with dilated sinuses and a relatively monotonous proliferation of small lymphocytes, plasma cells and plasmacytoid lymphocytes.

Cell of origin

WM is thought to arise from B-cells that are arrested after somatic hypermutation in the germinal center and before terminal differentiation to plasma cells [11, 12]. Analysis of the nature and distribution of somatic mutation in Ig heavy- and light-chain variable regions obtained from patients with WM indicate that WM may originate from an IgM+ and/or IgM+IgD+ memory B cell with a deficiency in the initiation of the switching process.

Genetics of WM

WM usually arises sporadically but about 20-25% of cases are familial with at least one first degree relative with WM or other B cell disorders [13]. Genome wide association studies have identified certain polymorphisms that increase susceptibility to multiple myeloma, Hodgkin lymphoma and CLL [14-16]. These polymorphisms may explain some of the familial associations seen in these disorders but similar variants have not been identified in WM. Genetic linkage analysis with WM families has shown an evidence of linkage on chromosomes 1q and 4q [17]. Population based studies have also shown an increased risk of WM and other lymphomas associated with auto-immune and other inflammatory conditions [18]. At this time the most important risk of developing WM is the presence of MGUS.

In WM, the malignant clone is characterized by specific epigenetic and genetic changes. The most common cytogenetic abnormality identified by FISH analysis is the deletion of 6q which was reported in up to 55% of cases [19, 20]. Other cytogenetic abnormalities including trisomy 4, trisomy 5, monosomy 8 and deletion of long arm of chromosome 20 have also been reported but deletion of long arm of 6 remains the most common chromosomal abnormality [21-23]. Among the candidate genes located on 6q, *BLIMP-1* is particularly interesting. It is a zinc finger containing protein that is important in the terminal differentiation of mature B cells into differentiated plasma cells [24]. Gene expression profiling of WM bone marrow samples has shown a homogenous transcription profile irrespective of the 6q deletion status [25]. Using SNP based array Poulain et al. detected copy number abnormalities in 75% of patients with partial deletion of 6q being the most common abnormality [26].

Array-based comparative genomic hybridization approaches showed that 83% of WM patients have chromosomal abnormalities with a median of three abnormalities per patient [27]. Gain of 6p was seen in 17% of patients and was always concomitant with 6q loss. A minimal deleted region, including miR-15a and miR-16-1, was delineated on 13q14 in 10% of patients. Biallelic deletions and/or inactivating mutations were observed with uniparental disomy in TNF receptor-associated factor 3 (*TRAF3*) and TNF α -induced protein 3 (*TNFAIP3*), two negative regulators of the NF- κ B signaling pathway. The study also found an association between TRAF inactivation and increased transcriptional activation of NF- κ B target genes highlighting a mutation driven mechanism of NF- κ B pathway activation.

Recently another mutation in the NF- κ B signaling pathway was identified by whole genome sequencing (WGS). Treon et al. performed WGS of bone marrow LPL cells in 30 patients with Waldenström's macroglobulinemia, with paired normal-tissue and tumor-tissue sequencing in 10 patients [28]. A single nucleotide variant was identified in the *MYD88* gene that predicted an amino acid change (L265P) in more than 90% of LPL samples tested. MYD88 L265P was absent in paired normal tissue samples from patients with WM or non-IgM LPL and in B cells from healthy donors. MYD88 is an adaptor molecule in toll-like receptor and interleukin-1 receptor activation of NF- κ B signaling. Ngo et al. have previously shown that *MYD88* mutations are present in about 40% of ABC type DLBCL [29]. This study also showed that MYD88 L265P, is a gain-of-function driver mutation, that promotes cell survival by spontaneously assembling a protein complex containing IRAK1 and IRAK4, leading to IRAK4 kinase activity, IRAK1 phosphorylation, NF- κ B signaling, JAK kinase activation of STAT3, and secretion of IL-6, IL-10 and interferon-beta. The role of MYD88 L265P in transforming IgM MGUS to WM will need further investigation. In the study by Treon et al. MYD88 L265P was present in only 10% of IgM MGUS patients, while in a small study Landgren et al. found the mutation in 5 of 9 patients (56%) [30]. Larger studies will be needed to ascertain whether MYD88 L265P is a transforming event that facilitates progression from IgM MGUS to WM and the overall role of the mutation in the pathogenesis of WM. Direct targeting of MYD88-IRAK signaling can be a potential novel therapeutic approach for patients with WM.

Epigenetic modifications in WM pathogenesis

In addition to the cytogenetic and genetic changes seen in WM, several studies have also examined the effect of epigenetic modifications as key regulators in the pathogenesis of WM. MicroRNA aberrations and modifications in histone acetylation status have been shown to play an important role in WM biology.

miRNA expression profiling of WM cells and normal B cells were compared using unsupervised clustering [31]. A WM-specific signature characterized by increased expression of miRNA-363*/-206/-494/-155/-184/-542-3p, and a decreased expression of miRNA-9*. miRNA-155 is expressed from an exon of the non-coding *BIC* gene and has been shown to be important in the initiation and progression of B-cell malignancies like DLBCL, primary mediastinal B-cell lymphomas and Hodgkin lymphoma [32, 33]. In this study, miRNA-155 was found to have an important functional role in WM cell proliferation, adhesion and migration. miRNA-155 knockdown, modulated cell cycle progression in WM cells, as demonstrated by an increased fraction of cells in G1-phase and decreased S-phase fraction. miRNA-155 knockdown was also shown to strongly inhibit ERK and AKT phosphorylation, as well as p-GSK3 α/β and p-S6R, both AKT downstream target proteins.

The role of miRNA-155 was also studied in the context of the BM microenvironment. A significant inhibition of adhesion to fibronectin was observed in the miRNA-155 knockdown cells compared with controls. This was further supported by the down-regulation of genes such as several Rho GTPase activating proteins, p21 (CDKN1A)

activating protein, and p21-activated kinase 1 (PAK1) interacting protein, which are known to be involved in the adhesion process. Similarly, miRNA-155 knockdown significantly inhibited WM cell migration in response to stromal derived factor-1 (SDF-1), an important regulator of migration in B cells. Using an *in vivo* homing model, the study also showed that miRNA-155 knockdown WM cells homed and proliferated in the bone marrow at a lower rate than control WM cells.

In a recent study, an 8-mer locked nucleic acid anti-miR-155 oligonucleotide targeting the seed region of miR-155 was shown to inhibit WM and CLL cell proliferation *in vitro* [34]. When delivered systemically, the anti-miR-155 showed uptake in BM CD19 (+) cells of WM-engrafted mice leading to decreased tumor growth significantly *in vivo*.

Histone acetylation is commonly deregulated in several tumors and alterations in the balance between histone acetyl transferase (HAT) and histone deacetylase (HDAC) activity in many cancers leads to deregulated gene expression and the induction of proliferation and survival in tumor cells [35]. Primary WM cells are characterized by unbalanced expression of HDACs and HATS, responsible for decreased acetylated histone-H3 and -H4, and increased HDAC activity [36]. HATs and HDACs expression is regulated by miRNA-206 and -9*. miRNA-206 expression is increased and miRNA-9* decreased in WM. In this study, restoring miRNA-9* levels induced apoptosis and autophagy in WM cells along with down-modulation of HDAC4 and HDAC5 and upregulation of acetyl-histone-H3 and -H4.

Role of bone marrow microenvironment in WM pathogenesis

In WM, there is continuous trafficking of cells in and out of the bone marrow leading to cell dissemination. The bone marrow microenvironment plays a crucial role in tumor cell proliferation, survival and drug resistance [37, 38]. The epigenetic and genetic changes described above may not be sufficient and a permissive microenvironment may be required for frank malignancy to emerge [39].

The role of bone marrow stromal cells (BMSCs) has been extensively studied in WM and other hematological malignancies. We and other have shown that stromal cells are critical for the growth of WM cells [40-42]. Additionally, co-culture of WM cells with stromal cells leads to resistance of WM cells to therapeutic agents including rituximab [40-42]. Endothelial cells also play an important role in WM cell growth. Ephrin-B2 (the ligand of Eph-B2 receptor, a tyrosine kinase) is highly expressed on endothelial cells from the BM of WM patients as compared to controls [43]. Eph receptors and ephrin ligands are overexpressed in several cancers and since both the receptor and ligand are membrane bound they play a role in cell-cell interaction. Activation of the Eph-B2 receptor with ephrin-B2 did not affect WM cell proliferation and cell cycle; however it induced activation of adhesion cascades that increased adhesion of WM cells to endothelial cells, which in turn, promoted WM cell proliferation through cell-cycle transition. The link between adhesion-regulating molecules and proliferative signaling pathways in WM is interesting and may lead to discovery of new therapeutic agents.

Several studies have focused on the role of cytokines in the pathogenesis of WM. In a recent study, Elsawa et al performed a comprehensive cytokine analysis on serum and bone marrow biopsy samples from WM patients and healthy donors. They found CCL5, G-CSF and soluble IL2 receptor elevated in WM patients while IL-8 and EGF levels were found to be lower as compared to healthy controls [44]. CCL5 levels were shown to correspond with disease aggressiveness in this study and there was a functional correlation between CCL5 and IL6 levels. IL6 is a proinflammatory cytokine and has a role in normal and malignant B cell biology and interestingly this study noted that CCL5 stimulated IL6 secretion in WM stromal cells resulting in increased IgM production by WM malignant cells via the JAK/

STAT pathway. Other cytokines that have been shown to be increased in WM include B-lymphocyte stimulator (BLyS) and macrophage inflammatory protein-1 alpha (MIP-1 α). Serum hepcidin levels are elevated among patients with WM as compared to healthy donors. Hepcidin levels positively correlate with BM disease involvement and inversely with hematocrit [45].

The migration of cells through the blood to the bone marrow niches requires active navigation through the process of homing. Homing is thought to be coordinated multistep process, which involves signaling by stromal derived factor (SDF-1), activation of lymphocyte function-associated antigen 1 (LFA-1), VLA-4/5, and activation of MMP2/9 [46]. WM cells express high levels of CXCR4 (a receptor for SDF-1) and VLA-4 [37]. CXCR4 is essential for the migration and trans-endothelial migration of WM cells under static and dynamic shear flow conditions, with significant inhibition of migration using CXCR4 knockdown or the CXCR4 inhibitor plerixafor. In whole genome sequencing studies CXCR4 variants were noted to be present in 6/30 (20%) patients [47]. Sanger sequencing confirmed WGS data and showed that the most common of these mutations was (C1013G) which confers gain of function including decreased CXCR4 internalization, more robust ERK1/2 phosphorylation, and chemotaxis [48]. Inhibition of CXCR4 leads to increased sensitivity of these cells to cytotoxicity by bortezomib. These studies highlight the importance of CXCR4 in the pathogenesis of WM and provide a strong rationale for the use of CXCR4 inhibitors in WM.

Primary treatment options for WM

There are no US Food and Drug Administration (FDA)-approved therapeutic agents for the treatment of WM. Treatment decisions are based on the presence of symptoms, patient factors including age and functional status and disease factors including presence of cytopenias, rate of disease progression, the level of IgM protein and the presence of neuropathy.

Current treatment options for WM include alkylating agents (e.g. chlorambucil, and cyclophosphamide), nucleoside analogue (fludarabine and cladribine), the monoclonal antibody rituximab, and the proteasome inhibitor bortezomib [49-51].

Rituximab is one of the most common agents used for the treatment of WM either as a single agent or in combination regimens. As a single agent it gives response rates of 35-48% [2, 52-54]. It is studied in combination with many agents including, cyclophosphamide, bendamustine, and bortezomib [55-59].

In a study by Dimopoulos, 72 patients with newly diagnosed WM received rituximab, oral cyclophosphamide and dexamethasone. Overall response rate (ORR), which includes minimal response or better, was 83%, including 7% complete response (CR), 67% partial remission (PR), and 9% minimal response (MR). The median time to progression was 35 months with a median overall survival (OS) of 95 months [55, 60].

In a phase III trial conducted by the Studygroup Indolent Lymphomas (StiL) which included 549 patients with low grade lymphomas, 162 WM patients were randomized to receive 6 cycles of bendamustine and rituximab (BR). Responding patients were randomized to rituximab every 2 months for 2 years or observation. Till August of 2012, ORR is 86% within the 116 evaluable patients. No uncommon toxicities were observed during BR induction [61].

Another rituximab combination studied in the upfront setting is 2 phase II studies one in combination with bortezomib and dexamethasone and the other in combination with

bortezomib only [57, 59]. The 3 drug combination was studied in 23 patients where bortezomib was given on the twice weekly regimen. ORR was 96%, with 3 patients in CR, 2 nCR, 3 VGPR, 11 PR, and 3 MR. In this study peripheral neuropathy (PN) was the most common toxicity with 30% of patients experiencing grade 3 PN [57]. In the study without the use of dexamethasone by Ghobrial et al., bortezomib was given as once a week injection. ORR was 80-90% and patients developed minimal PN [59].

New developments in WM

With the new advances in our understanding of the pathogenesis of WM, many novel therapeutic agents are showing activity against WM cells. These include PI3K/mTOR inhibitors, new generation proteasome inhibitors, BTK inhibitors, HDAC inhibitors, and IMiDs. Some of these are in clinical trials while some have shown preclinical efficacy and clinical trials are still to follow.

PI3K/AKT/mTOR pathway inhibitors

Based on in-vitro data which showed increase in activity of the PI3K/mTOR pathway in WM, several clinical trials are studying the effect of inhibiting these pathways [62].

A phase II trial of single agent everolimus was studied in 50 patients with relapsed/refractory WM. Everolimus (RAD001) is an inhibitor of MTORC1, a component of the Akt-MTOR pathway which regulates growth and survival of lymphoplasmacytic cells in WM. The overall response rate was 70% with a PR of 40% and MR of 30%. The most common adverse events were cytopenias. Pulmonary toxicity, which is a serious adverse effect of everolimus, was seen in 10% of patients [63]. Another phase I/II study of everolimus in combination with bortezomib and/or rituximab in relapsed/refractory patients showed ORR of 74%. Complete response was seen in 5% of patients with PR of 30% and MR of 39% [64]. A prospective, multicenter Study of everolimus as primary therapy was conducted in 33 WM patients. The best overall response rate utilizing consensus criteria was 66.7% (14 partial responses, 8 minor responses, and 11 stable disease), for a major response rate of 42.4%. Grade 2 toxicities included anemia (24%), thrombocytopenia (15%), neutropenia (15%), hyperglycemia (6%), oral ulcerations (21%), pneumonitis (15%), fatigue (12%), rash (6%), and cellulitis (6%). With a median follow-up of 9 months (range 0-18 months), 15 patients remain on study [65] (see table 1).

A phase I trial of the new agent MLN0128 was studied in 37 patients with relapsed/refractory WM/MM or NHL. MLN0128 is an investigational oral, selective, ATP site inhibitor of the mTOR complexes TORC1 and 2. Among the 27 evaluable patients, 1 patient achieved MR lasting 2 months, and 15 patients had stable disease. Fourteen patients discontinued therapy because of progressive disease, and 27% discontinued because of adverse events. Overall, 43% of patients had grade 3/4 adverse events, including thrombocytopenia (16%), fatigue (8%), mucosal inflammation (5%), and neutropenia (5%) [66].

A phase II trial of enzastaurin was studied in 42 patients with WM who were previously treated with 1 to 5 regimens. Enzastaurin is an oral serine/threonine kinase inhibitor that targets the PKC and PI3/AKT pathway. The objective response rate was 38.1%, with 2 patients achieving PR and 14 achieving minor response. Grade 3 adverse events seen were leukopenia in one patient and septic shock in another one [67].

Another phase II trial was conducted with perifosine, an alkylphospholipid that targets Akt. This trial included 37 patients with WM who were previously treated with 1 to 5 regimens. The objective response rate (MR or better) was 35% with 11% achieving PR and 24%

achieving MR. Progressive disease was observed in only 11% of patients since 54% had stable disease. The most common adverse events were GI toxicities including diarrhea, nausea and vomiting [68].

CAL-101, an oral isoform-selective inhibitor of PI3K δ that inhibits PI3K signaling and induces apoptosis of NHL cell lines in vitro, was studied in a phase I trial in 55 patients with relapsed/refractory NHL which included 4 patients with WM. Overall response rate was 62% in patients with indolent NHL. Grade 3 adverse events were hematologic and increase in liver enzymes [69].

Proteasome Inhibitors

Carfilzomib, a second generation proteasome inhibitor which was approved by the FDA in July of 2012 for the treatment of patients for relapsed/refractory myeloma is also being studied in WM. Antitumor activity of carfilzomib was validated in vivo by Sacco et al who demonstrated that carfilzomib targeted the chymotrypsin-like (CT-L) activity of both constitutive-(c20S) and immuno-(i20S) proteasome, which led to the induction of toxicity in primary WM cells, as well as in other IgM-secreting lymphoma cells [70].

The preliminary results from the CaRD trial by Treon et al showed that carfilzomib in combination with rituximab and dexamethasone is an active treatment for symptomatic patients with WM and produces rapid responses. Among the 20 patients assessed, 16 were previously untreated and 4 had prior therapies. The overall response rates and major response rates were 75% and 50% with one very good partial response, 9 partial responses, and five minor responses. With a median follow-up of 5 months, 14 of 20 patients are free of disease progression. Most common toxicities which were grade 2 were hyperglycemia (50%); asymptomatic elevation of lipase (35%); and hypersensitivity (30%). All toxicities were reversible, and no grade 2 peripheral neuropathy was observed [71].

Immunomodulatory Drugs

Thalidomide and lenalidomide are studied in combination with Rituximab in symptomatic WM patient [72, 73]. A phase 2 study was conducted using thalidomide (200 mg for 2 weeks, then 400 mg for a total of 1 year) and Rituximab. A total of 25 patients were included, 20 of whom were previously untreated. Overall and major response rate were 72% and 64%, respectively, with complete response (n = 1), partial response (n = 15), and major response (n = 2). Median time to progression for responders was 38 months. With peripheral neuropathy being the most common adverse event (grade 2 in 44%), the authors concluded that lower doses of thalidomide (< 200 mg/day) should be considered given the high frequency of treatment-related neuropathy in this patient population [72]. Lenalidomide 25mg/d was tested in combination with rituximab in 16 patients, 12 of whom were previously untreated. The overall response and major response (<50% decrease in serum IgM) rates were 50% and 25%, respectively, with a median time to progression of 18.9 months. Premature discontinuation of lenalidomide therapy occurred in 14 of 16 (88%) patients which was most commonly due to an acute decrease in hematocrit in 13 of 16 patients (median hematocrit decrease, 4.8%), which resulted in 4 patients requiring hospitalizations due to anemia complications. This was attributable to lenalidomide and led to cessation of further enrollment on this study [73]. Phase I trials of lenalidomide and the novel immunomodulatory agent pomalidomide are ongoing.

Histone-Deacetylase Inhibitors (HDACi)

In vitro studies have confirmed the antitumor activity of panobinostat (HDACi) in primary tumor cells and cell lines [74]. A phase II trial of panobinostat was studied in 27 patients with relapsed or relapsed/refractory WM. Overall response rate has been achieved in 15

(60%) of patients, with 6 (24%) PR, 9 (36%) MR. In addition, 9 (36%) patients achieved stable disease and 1 (4%) showed progression. Grade 3 and 4 toxicities include anemia (15%), grade 4 leucopenia (3%), neutropenia (26%), thrombocytopenia (52%), and grade 3 fatigue (27%). Further studies are under way to better define the efficacy of HDAC inhibitors in WM [75].

Bruton Tyrosine Kinase (Btk) inhibitor

B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation. Bruton's tyrosine kinase (Btk) is an essential element of the BCR signaling pathway. Inhibitors of Btk, like ibrutinib (previously PCI-32765), is an oral selective and irreversible small molecule Btk inhibitor that blocks BCR signaling and induces apoptosis [76]. A phase I study of ibrutinib was conducted in 56 patients with a variety of B-cell malignancies. Objective response rate in 50 evaluable patients was 60%, including complete response of 16%. Median progression-free survival in all patients was 13.6 months. Partial responses were seen in 3 of the 4 patients with WM and the drug was well tolerated [77]. A phase 2 trial is initiated to determine response in patients with relapsed or refractory WM.

Future Developments

Preclinical efficacy has demonstrated anti WM activity with new PI3/Akt/mTOR inhibitor BEZ-235, and the new proteasome inhibitor Onyx 0912 (Oprozomib) either in vivo or in vitro [40, 78].

In a recent study using the PI3K/mTOR inhibitor NVP-BEZ235, Roccaro et al showed that BEZ235 exerts antitumor activity by inhibiting phosphorylation of important proteins that act as key regulators of adhesion and cell migration, and inhibits homing of WM cells to the BM in vivo. BEZ235 is also being studied in solid tumors, including advanced breast cancer, metastatic castrate resistant prostate and advanced renal cell carcinoma [40].

Roccaco et al also studied Onyx 0912, a novel selective irreversible inhibitor of the CT-L activity of i20S and c20S which led to induction of toxicity in primary WM cells, as well as apoptosis. Onyx 0912 is an oral agent that is being studied as a phase I/II trial in hematologic malignancies including WM [78].

Many studies are ongoing and they include combinations of several agents. An Eastern Cooperative Oncology Group trial is studying the addition of temsirolimus to the regimen bortezomib, rituximab, and dexamethasone for patients with untreated or relapsed WM or relapsed or refractory mantle cell or follicular lymphoma. Dimopoulos is studying the combination of bortezomib, dexamethasone, and rituximab in previously untreated patients with WM. Ofatumumab in combination with bortezomib is being studied in patients with previously untreated WM.

Conclusion

Many new agents have emerged in the last couple of years for the treatment of WM. These newer agents improve responses and reduce long term toxicities. However, better understanding of the biology of the disease can further improve outcomes. Whole genome sequencing studies are helping to identify specific mutations in subgroups of patients with WM. Understanding the role of the epigenetic modifications and how to target these changes are being examined. In addition, the role of the bone marrow environment which plays a crucial role in tumor cell proliferation, survival and drug resistance is being studied. These advances in the understanding of the underlying pathogenesis of WM, will lead to the development of novel therapeutic agents and targeted therapies for patients with this disease.

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Table 1

Phase II studies of the new agents in WM

Study	Regimen	Patients	N	ORR %	MR	PR	CR
Ghobrial [63]	RAD001	Relapsed or Refractory	50	70	30	40	0
Ghobrial [64]	RAD001/Rituximab/bortezomib	Relapsed or Relapsed/ Refractory	23	74	39	30	5
Treon [65]	RAD001	Primary therapy	33	66.7	24.3	42.4	0
Ghobrial [67]	Enzastaurin	Previously treated	42	38.1	33.3	4.8	0
Ghobrial [68]	Perifosine	Relapsed or Relapsed/ Refractory	37	35	24	11	0
Treon [71]	Carfilzomib/Rituximab/Dexamethasone	Symptomatic	20	75	25	45	0
Ghobrial [75]	Panobinostat	Relapsed or Relapsed/ Refractory	27	60	36	24	0

MR: Minimal response; PR: Partial remission; CR: Complete response

ORR: Overall response rate (complete response + partial remission + minimal response)