

REVIEW ARTICLE

Update on therapeutic options in Waldenström macroglobulinemia

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Abstract

Waldenström macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells (LPCs), along with demonstration of an IgM monoclonal gammopathy in the blood. WM remains incurable, with 5–6 yr median overall survival for patients with symptomatic WM. The main therapeutic options include alkylating agents, nucleoside analogues, and rituximab, either in monotherapy or in combination. Studies involving combination chemotherapy are ongoing, and preliminary results are encouraging. However, there are several limitations to these approaches. The complete response rate is low and the treatment free survival are short in many patients, no specific agent or regimen has been shown to be superior to another, and no treatment has been specifically approved for WM. As such, novel therapeutic agents are needed for the treatment of WM. In ongoing efforts, we and others have sought to exploit advances made in the understanding of the biology of WM so as to develop new targeted therapeutics for this malignancy. These efforts have led to the development of proteasome inhibitors, of them bortezomib, several Akt/mTor inhibitors, such as perifosine and Rad001, and immunomodulatory agents such as thalidomide and lenalidomide. Many agents and monoclonal antibodies are currently being tested in clinical trials and seem promising. This report provides an update of the current preclinical studies and clinical efforts for the development of novel agents in the treatment of WM.

Key words Waldenström macroglobulinemia; novel therapy

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Accepted for publication 5 October 2008

doi:10.1111/j.1600-0609.2008.01171.x

Waldenström macroglobulinemia (WM) is a distinct low grade B-cell lymphoma characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of a serum IgM monoclonal gammopathy (Table 1) (1). This disease was later classified as a low grade B-cell non-Hodgkin lymphoma under the Revised European American Lymphoma and World Health Organization classification. WM was first described by Dr. Jan Waldenström in 1944. WM has an overall incidence of approximately 3 per million persons per year, accounting for approximately 1–2% of hematological cancers, and approximately 1500 new cases diag-

nosed per year in the USA (2, 3), however, this incidence might be underestimated because many patients are not diagnosed due to lack of symptoms at early stages of the disease. The median age varies between 63 and 68 yr, with 55–70% men (4, 5). The incidence of WM is higher among whites, with blacks representing only 5% of all patients (6). WM is believed to be predominantly a sporadic disease; however, studies have demonstrated a high familial incidence of this disease, with about 18% of the patients having at least a first degree relative with a B-cell neoplasm (7). The main risk factor for the development of WM is preexisting IgM-monoclonal

Table 1 Diagnostic criteria for Waldenström macroglobulinemia (1)

IgM monoclonal gammopathy of any concentration
Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation
Intertrabecular pattern of bone marrow infiltration
Cell Surface Markers
IgM ⁺ CD5 ⁺ CD10 ⁻ CD19 ⁺ CD20 ⁺ CD22 ⁺ CD23 ⁻ CD25 ⁺ CD27 ⁺ FMC7 ⁺ CD103 ⁻ CD138 ⁻ Variations from this phenotypic profile can occur.

gammopathy of undetermined significance (MGUS), which confers 46 times higher relative risk than for the general population (8). Morra *et al.* (9) also showed a progressive increase in the risk of transformation from asymptomatic IgM-MGUS to symptomatic WM, with increasing IgM levels.

Despite advances in therapy, WM remains incurable and most patients die of disease progression. The median overall survival of patients with WM is 5–6 yr; however a recent study in patients with symptomatic WM, demonstrated median disease specific survival of 11.2 yr (10). Ongoing efforts to understand the biology of WM have led to the development of new targeted therapeutic agents that are currently being tested in clinical trials and seem promising. This report provides an update of the current preclinical studies and clinical efforts for the development of novel agents in the treatment of WM.

Diagnosis and clinical aspects

The origin of the malignant clone is thought to be a B-cell arrested after somatic hypermutation in the germinal center, before terminal differentiation to plasma cells (11). Post-switch clonotypic Ig (IgG or IgA) is undetectable in WM B cells, confirming the absence of isotype switch events by deletional recombination. WM cells have normal class switch recombination machinery, but defective initiation of the switching process. Furthermore, analysis of 14q32 rearrangement demonstrates that WM cells lack IgH (Ig heavy chain) rearrangement (12, 13). Deletion of the long arm of chromosome 6 (6q-) is the most frequent cytogenetic abnormality in WM (14). The WM clone is characterized by intratrabecular infiltrates of lymphocytes, lymphoplasmacytoid lymphocytes and plasma cells (15). The cells express pan B-cell markers including CD19, CD20 and CD22, but lack CD10, CD38, FMC7, and cytoplasmic Ig (16). CD5 and CD23 are expressed in 5–20% and 35% of the cases respectively (17).

WM is a heterogeneous disease and patients can present with a broad spectrum of symptoms and signs (4, 18, 19). Most patients with the diagnosis of WM have symptoms attributable to tumor infiltration, to circulating IgM, to tissue deposition of IgM, and to autoantibody activity of IgM. The most common clinical presentations

Table 2 Differential diagnostic of WM (20)

Differential diagnostic	Characteristic features
SMZL	CD22, CD11c overexpressed with SMZL, whereas CD25 was more common in WM(88% vs. 44%). Loss of 7q along with +3q and +5q in SMZL
IgM-MGUS	No morphologic evidence of bone marrow infiltration at trephine biopsy however possible detectable bone marrow clonal B cells by flow cytometry 6q- suggested marker to distinguish WM from IgM-MGUS
IgM-MM	Pure plasma cell morphology in myeloma and presence of lytic bone lesions in myeloma
B-cell CLL	Lymphocytes typically small and mature, without visible nucleoli, and smudge cells Lymphocytes in CLL are positive for CD5 and CD23
Mantle cell lymphoma	Bone marrow infiltration by monomorphous small-medium lymphoid cells, with irregular nuclei and presence of involves lymphonodes, and extranodal sites such as gastro-intestinal tract and spleen and t(11;14) (q13;q32)

are related to cytopenias, specifically anemia related to replacement of the bone marrow with tumor cells. Fatigue is a very common presentation of WM that is multifactorial, due at least in part to the underlying degree of cytopenias. Patients may also present with symptoms of hyperviscosity related to elevated IgM levels including headache, blurring of vision, and epistaxis. Hepatosplenomegaly and lymphadenopathy occur in 20% of the patients, and some patients may present with B symptoms including night sweats, fever, and weight loss.

Differential diagnoses are summarized in Table 2. It is possible to find an IgM monoclonal component accompanied by a bone marrow infiltration of lymphoplasmacytic cells in other B-cell lymphoproliferative disorders, besides WM, including, multiple myeloma (MM), B-cell chronic lymphocytic leukemia (CLL), mantle cell lymphoma, follicular lymphoma, and splenic marginal zone lymphoma (SMZL) (20).

Several studies have evaluated the effects of different clinical and laboratory variables on patient outcome (21), and demonstrated that serum IgM level does not reflect in a sensitive and accurate fashion the tumor burden or prognosis in WM. Factors associated with poor prognosis in patients with WM include: advanced age, high β 2-microglobulin, cytopenias, low albumin, and organomegaly (5, 10, 22). An International Prognostic Scoring System was presented at the 2006 American Society of Hematology panel as a staging system for survival for symptomatic patients in need of therapy (23). The parameters used to stratify risk were age older than 65 yr, β 2-microglobulin level > 3 mg/L, monoclonal protein > 70 g/L, hemoglobin < 11.5 g/dL, and platelet count < 100×10^9 /L. Low risk was defined as the

Table 3 International Prognostic Scoring System (WM-IPSS) (23)

	Risk		
	Low	Intermediate	High
Age > 65 yr	-	+ or	
Hb ≤ 11.5 g/dL	} ≤ 1 factor	} 2 factors	} > 2 factors
Platelet ≤ 100 × 10 ⁹ /L			
β2m > 3 mg/L			
IgM > 70 g/L			
N (%)	158 (27)	223 (38)	206 (35)
Survival at 5 yr (P < 0.001)	87%	68%	36%

Hb, hemoglobin; β2m, beta2-microglobulin; N, number of patients; %, percentage.

presence of fewer than one adverse characteristic except age; high risk, as the presence of more than two adverse characteristics; the remaining patients with two adverse characteristics or older than 65 yr had intermediate risk (Table 3). Other markers currently studied are the serum free light chain (24) and the serum soluble CD27 (85).

Initiation of therapy and response criteria

The Third International Workshops on WM confirmed that patients should receive therapy only if they have symptoms or signs related to WM or specific laboratory abnormalities, and not based only on the serum monoclonal protein level (19, 26). Initial presenting symptoms vary and include fatigue, weight loss, anorexia or general malaise. Alternatively, patients may present with an asymptomatic rise in serum protein level. Classically, patients can present with symptoms of hyperviscosity, particularly when the IgM level exceeds 30 g/L. Symptoms include epistaxis, blurred vision, dyspnea or headache. Immune complex phenomenon from the IgM protein may also occur, leading to peripheral neuropathy, cold agglutinin hemolytic anemia, cryoglobulinemia, or Raynaud’s phenomenon. The most common indication for initiation of therapy is anemia (10).

Assessment of response to treatment in WM has been widely heterogeneous. As a consequence studies using the same regimen have reported significantly different response rates. As part of the second and third International Workshops on WM, consensus panels developed guidelines for uniform response criteria in WM (27). The category of minor response was adopted at the Third International Workshop of WM. In distinction, the term major response is used to denote a response of ≥ 50% in serum IgM levels, and includes partial and complete responses. An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate, independent of tumor cell killing, particularly with newer biologically targeted agents such as rituximab and

bortezomib (28, 29). In circumstances where the serum IgM levels appear out of context with the clinical progress of the patient, a bone marrow biopsy should be considered in order to clarify the patient’s underlying disease burden.

Conventional therapeutic

There is no standard of therapy and no Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved therapeutic agents for the specific treatment of WM. Most treatment options were originally derived from other lymphoproliferative disease including MM and CLL. As part of the Third International Workshop on WM a consensus panel charged with providing treatment recommendations for WM updated its recommendations on both frontline and salvage therapy (19, 26). In frontline, the use of alkylator drugs, nucleoside analogues such as fludarabine or cladribine, the monoclonal antibody rituximab, as well as combinations of these agents have resulted in response rates of 30–90%. Notable however, has been the lack of complete responses (CR) with the use of these agents or regimens in the frontline setting, with CR rates of 8–10% observed. However, the panel recommended that for patients who may be eligible for autologous transplant, exposure to alkylating agents and nucleoside analogues should be limited in view of reports suggesting depletion of stem cells by these agents (26). The current hurdle is to define the standard treatment in WM in frontline and continue to develop new therapeutic options to improve the rate of complete responses. For patients with relapsed disease, the use of alternate first-line agents, re-use of a first-line agent, use of combination myelotoxic chemotherapy, and the use of thalidomide as a single agent or in combination therapy were recommended in the Third International Workshop on WM (19, 26).

Major therapeutic agents in WM

Purine nucleoside analogues

Cladribine and fludarabine have been extensively studied in WM and induced overall response rates that ranged from 40 to 100% in previously untreated and treated WM patients, with prolonged survivals (30, 31); Leblond, 2001 #987]. Fludarabine therapy was administered mainly on 5-d schedules. Similar results were reported with Cladribine (32). There is limited experience in the use of an alternate nucleoside analogue to salvage patients whose disease relapsed after cladribine or fludarabine therapy. The main complications of these agents are myelosuppression and immunosuppression, especially of T cells, leading to an increased risk of infections and a treatment-related mortality of up to 5% in some series.

In addition, stem cell collection may also be problematic after prolonged exposure to purine nucleoside analogues. The long-term safety, especially evolution of WM to diffuse large B-cell lymphoma (DLBCL) as a result of histologic transformation, of nucleoside analogues in WM has been recently examined in a large series of WM patients (33). A seven-fold increase in transformation to an aggressive lymphoma/myelodysplasia was observed among patients who received a nucleoside analogue vs. other therapies for WM. Onset of DLBCL is usually characterized by an aggressive clinical course, however, the outcome of this complication, although controversial, might be better upon CHOP-R (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituximab) regimen (33, 34). The clinicopathologic features at diagnosis of WM do not predict the risk of DLBCL (34).

Rituximab

Response rates to single agent rituximab are low and vary between 20% and 50% (35, 36). The response to rituximab is delayed in most patients with a median time to partial response of 4 months and a median time to best response of 17 months. Polymorphisms in the Fc γ RIIIA (CD16) receptor gene may affect response to rituximab (37, 38). Transient increases in IgM titers (also called IgM flare) have been reported in 54% of patients after initiation of rituximab therapy. These levels may persist for up to 4 months and do not indicate treatment failure, but they may necessitate plasmapheresis to reduce hyperviscosity. Patients who had initial IgM flares had worse response rates compared to those with lower IgM levels (28% vs. 80%) (39). New protocols tend to combine other therapeutic to rituximab in order to better control occurrence of IgM flare. The impact of maintenance therapy with rituximab on the time to progression has not been validated specifically in WM, as compared with other low-grade lymphomas in which prolonged time to progression is described (40). Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG auto antibody-related neuropathies (41).

Combination regimens

Nucleoside analogues-based combination regimens have included the combination of rituximab and fludarabine, of oral cyclophosphamide with either cladribine (32) or fludarabine (42, 43), and the combination of fludarabine and cyclophosphamide to rituximab (FCR) (44). Overall response rates ranged from 50 to 90% at diagnosis as a relapse, with a low CR rate of less than 10%, and a median duration of response that vary from 27 to 36 months. Delayed responses (4 to 10 months) were also observed in almost half the patients in some series.

Table 4 Combination therapies in WM including nucleoside analogues with alkylating agents and rituximab

Study	Regimen	N	Phase	ORR %
Tam (96)	Fludara/CTX	9	II	88
Tamburini (43)	Fludara/CTX	49	II	78
Weber (32)	Cladribine/CTX	37	II	84
Tam (44)	Fludara/CTX/rituximab	5	II	80
Weber (32)	Cladribine/CTX/rituximab	27	II	94
Hensel (97)	Pentostatin/CTX/rituximab	17	II	90

Phase, phase of study; N, number of patients; ORR, overall response rate; CR, complete response; %, percentage.

Response rates, and especially CR rates, vary in CLL depending on the regimen used and the length of the treatment, 3 or 5 d. A larger experience is therefore needed, and an increase number of patients have to be treated with this regimen using the different modalities of administration of RFC regimen before a definite picture of response rates and survival can be determine with nucleoside analogues-based combination regimens. Hematological toxicity was again commonly observed. Table 4 summarized response rates in the different regimen that combined addition of alkylating agents to nucleoside analogs and rituximab.

Alkylating-based combination regimens were studied in association with anthracyclins, either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (45) or CHOP-R (46, 47), or without anthracyclins such as DRC (dexamethasone, cyclophosphamide and rituximab) (48). Overall response rates ranged from 70 to 94% with benefit to addition of rituximab (47), but CR rates are again lower than 10% (46). Treatment regimens were well tolerated and the main toxicity observed was grade 3–4 neutropenia in approximately 20% of the patients.

Other options

Chlorambucil was the first agent used, usually as a single agent, with response rates varying between 31% and 92% (49). The current use of chlorambucil in clinical practice has decreased due to the development of long term complications such as myelodysplasia and acute leukemia from therapy-induced chromosomal breakage (50). In addition, stem cell damage due to therapy may prevent collection of stem cells. Although chlorambucil is a treatment that has proven efficacy in WM, its use should only be recommended for patients with limited therapeutic options. The use of rituximab in combination with chlorambucil is under consideration in other low grade lymphoma, and could be an option of therapy for patients with WM (51).

High-dose chemotherapy with autologous stem cell rescue in primary refractory or relapsed disease should be considered for eligible patients (19, 26), although few

studies are available. Different conditioning regimens were proposed and none appeared superior. Either a high dose melphalan-based regimen as proposed in MM (52) or a BEAM (BCNU, etoposide, cytarabine, melphalan)-based regimen as proposed in NHL (53, 54) are reasonable choices. A study of 18 highly treated WM patients in France who received high-dose chemotherapy followed by autologous stem cell transplantation was recently reported and showed an acceptable tolerance and an improvement in response status with a median event-free survival for all non-progressing patients of 12 months. This procedure seems to give the highest complete response rate so far, but whether it prolongs survival durations is still a matter of debate.

Allogeneic and 'non-myeloablative allogeneic' transplantations should be cautiously approached, given the associated high mortality and/or morbidity risks, and should be undertaken only in context of a clinical trial (19, 26). Tournilhac *et al.* (55) have reported the outcome of allogeneic transplantation in 10 previously treated WM patients (ages 35–46 yr) who received a median of three prior therapies, including three patients with progressive disease despite therapy. The median event-free survival for non-progressing evaluable patients was 31 months. Concerning in this series was the death of three patients owing to transplantation related toxicity. A second series was published (56) on a retrospective review of WM patients who underwent allogeneic transplantation at relapse. The relapse rate at 3 yr was 29% in the allogeneic group. Non-relapse mortality however was 40% in the allogeneic group.

Plasma exchange and splenectomy are only symptomatic therapy. Plasma exchange (1–1.5 volume) is indicated for the acute management of patients with symptoms of hyperviscosity because 80% of the IgM protein is intravascular. Splenectomy is rarely indicated, but limited case reports suggest that it may be helpful for managing symptomatic painful splenomegaly and hypersplenism.

Novel therapeutics agents

Proteasome inhibitor bortezomib

Proteasomal degradation is the main mechanism accounting for intracellular protein degradation. The prototype 26S proteasome inhibitor bortezomib (Velcade®; Millenium The Takeda Oncology Company, Cambridge, MA, USA) selectively binds to the catalytic domain of the proteasome and prevents its activity. (57) Proteasome inhibitors such as bortezomib have become the focus of clinical research in many malignancies including WM. Based on its activity in MM, single agent bortezomib was tested in WM in phase II trials using the standard FDA approved schedule (58–60). In the NCI-Canada study,

Chen *et al.* observed 78% overall response rate, with major responses observed in 44% of patients, however, sensory neuropathy occurred in 20 patients, five with grade > 3, and occurred following 2–4 cycles of therapy. Among the patients developing a neuropathy, 14 patients resolved following cessation of therapy. These results were confirmed in a multi-center study of the Waldenström macroglobulinemia Clinical Trials Group (WMCTG) in relapsed WM patients (58). Responses occurred at a median of 1.4 months. The median time to progression for all responding patients in this study was 7.9 months, and the most common grade 3/4 toxicity was sensory neuropathies (22.2%). Herpes zoster prophylaxis is needed in patients with WM as recommended in myeloma. An interesting observation with the use of bortezomib in a subset of WM patients has been the discordance observed between serum IgM levels and bone marrow responses, suggesting that for these patients bortezomib may be inhibiting IgM secretion independent of direct tumor cell killing (58). Other proteasome inhibitors are in their first phase of development in WM, NPI-0052 (Nereus Pharmaceuticals, San Diego, CA, USA) (61) and PR171 (Proteolix, San Francisco, CA, USA) (62).

The addition of rituximab as well as steroids to bortezomib has been the subject of clinical investigation in WM disease. In a trial by the WMCTG, bortezomib has been combined with dexamethasone and rituximab (BDR) for the primary therapy of patients with WM. The development of peripheral neuropathy occurs in up to half of patients and the trial was stopped (63). Interestingly, Dr Ghobrial is conducting another phase II trial for relapse WM patients at DFCI that examine the use of weekly intravenous bortezomib at 1.6 mg/m² along with rituximab (at 375 mg/m²) in patients. The overall response rate was over 80% in the first 17 evaluable patients. This study has been expanded to also include an arm of newly diagnosed patients to determine the toxicity and efficacy of once a week bortezomib therapy in patients with newly diagnosed WM, the final results will be presented at ASH 2008.

The immunomodulatory agents (IMiDs)

In view of their success in the treatment of patients with MM (64), IMiDs were tested in patients with WM, although their experience is limited.

Thalidomide

Thalidomide is non-myelosuppressive, immunomodulatory, and antiangiogenic that has prove strong efficacy in relapse and even refractory MM patients following several courses of therapy (65). Studies to evaluate thalidomide alone or in combination with either clarithromycin

(66) or rituximab (67) as well as steroids have shown interesting partial response rates that ranged from 25 to 83%. Adverse effects were common with thalidomide treatment and prevented dose escalation of thalidomide in 75% of patients. Although previous study have demonstrated that thalidomide significantly augmented rituximab mediated antibody dependent cell mediated cytotoxicity against lymphoplasmacytic cells (68), response rates did not significantly improved. With a median follow-up of 42+ months, the median time to progression (TTP) for responders was 38+ months. Thalidomide might be a reasonable choice for patients for whom first-line therapies have failed, those who have had disease relapse and are not candidates for alkylating or nucleoside analogue therapy, or patients with pancytopenia.

Lenalidomide

Lenalidomide has been studied in multiple myeloma and myelodysplastic syndrome and found to be more potent and also to lack the neurotoxic and prothrombotic adverse effects of thalidomide. Similarly, based on the potent activity of lenalidomide in MM and the lack of neuropathy with this agent, Dr Treon conducted at DFCI a phase II study of lenalidomide 25 mg daily in combination with rituximab in patients with relapsed or relapsed/refractory WM. Acute decrease in hematocrit was observed during first 2 wk of lenalidomide therapy in 13/16 (81%) patients with a median hematocrit decrease of 4.4% (1.7–7.2%), resulting in hospitalization in four patients. Despite reduction of initiation doses to 5 mg daily, anemia continued to be problematic without evidence of hemolysis or more general myelosuppression. Therefore, the mechanism for pronounced anemia in WM patients receiving lenalidomide remains to be determined and the use of this agent among WM patients remains investigational.

Monoclonal antibodies

Alemtuzumab (MabCampath)

Alemtuzumab (ILEX Oncology, San Antonio, TX, USA) is a humanized monoclonal antibody which targets CD52, an antigen widely expressed on bone marrow lymphoplasmacytic cells (LPCs) in WM patients, as well as on mast cells which are increased in the bone marrow of patients with WM (69, 70). A phase II study of alemtuzumab was conducted in 25 patients with relapsed or newly diagnosed untreated WM (71). Alemtuzumab was administered following the regimen used in CLL, 30 mg alemtuzumab IV three times a week for up to 12 wk. All patients received acyclovir and bactrim prophylaxis for the duration of therapy plus 8 wk following the last

infusion of alemtuzumab. All patients completed a median of 33 infusions (range 10–36) post test-dosing. WM patients showed an overall response rate of 76%, which included eight (32%) major responders. Hematological toxicities were common among previously treated (but not untreated) patients. G3/4 non-hematological toxicity for all patients included dermatitis (11%); fatigue (7%); and infection (7%). Cytomegalovirus reactivation and infection was commonly seen among previously treated patients. With a median follow-up of 8.5+ months, 11/19 responding patients remain free of progression. High response rates are observed (69) with the use of alemtuzumab, but treatment related mortality is unacceptable, especially in the context of salvage therapy.

Radioimmunotherapy

Radioimmunotherapy directed to CD20 (90Y-Ibritumomab tiuxetan, Zevalin®; IDEC Pharmaceuticals Corporation, San Diego, CA, USA) or iodine 131 tositumomab (Bexxar®; GlaxoSmithKline, Philadelphia, PA, USA) in WM has been limited since the high level of bone marrow involvement precludes their use. However, case reports have shown that these therapies may be effective in patients with WM who have < 25% bone marrow involvement (72). Epratuzumab (Amgen Inc., Thousand Oaks, CA, USA) is a new radio-conjugated humanized monoclonal antibody anti-CD22 currently in development in non-Hodgkin high grade and indolent lymphomas. Further experiences are required before to test this new agent in WM, but there is hope that this agent might add to the therapeutic options in WM in the future.

Signaling pathways inhibitors. PI3K/Akt/mTOR pathway inhibitors

PI3K pathway, including Akt (73, 74), mTOR (75) and PKC (76) has been involved in survival and proliferation of several cancer types along with WM. This pathway is therefore a target for therapy in WM (77).

Perifosine

Perifosine (Keryx Biopharmaceuticals, New York, NY, USA) is a novel Akt inhibitor that belongs to a class of lipid-related compounds called alkylphospholipids and has shown some activity in phase II trials in MM (78). A phase II trial of single agent perifosine in patients with relapsed or relapsed/refractory disease using 150 mg oral daily dosing was conducted. Results were reported at ASCO 2008 (79). The trial completed accrual of 36 evaluable patients, of these 65% were relapsed and 35% were relapsed and refractory to prior therapy. The overall response rate was 35%, with two (5%) major

responses, and 11 (30%) minor responses. The progression free survival and TTP are similar with a median of 10.7 months. The overall response rate in 36 patients with WM was 35%. Perifosine was generally well tolerated. The main toxicities observed were gastrointestinal side effects including nausea, vomiting, and mild diarrhea. Interestingly, arthritis flare occurred in three patients who achieved rapid response to therapy.

mTOR inhibitors

A phase II trial of single agent RAD001® (Everolimus; Novartis, Cambridge, MA, USA) (orally at 10 mg daily) was initiated in patients with relapsed or refractory WM at DFCI by Dr IM Ghobrial (80). To date, 35 patients have been enrolled and preliminary results are showing exciting activity even in the relapsed setting.

PKC inhibitor, enzastaurin (Eli Lilly, Indianapolis, IN, USA)

A phase II clinical trial of enzastaurin in patients with relapsed or refractory WM has been initiated.

Other therapeutic options

Imatinib mesylate (Gleevec®)

Imatinib (Novartis) targets the microenvironment of WM through inhibition of stem cell factor signaling through CD117, which is expressed on WM tumor cells (16). A phase II trial of single agent imatinib was performed in patients with relapsed or refractory WM (81). Imatinib was given at 400 mg daily, with dose escalation to 600 mg after 1 month of therapy, for up to 2 yr. After 3 months of therapy 46.2% of patients achieved minor response. Responses were prompt, and occurred at a median of 2.5 months. The main toxicities observed included cytopenias, edema, and hyperglycemia, leading to dose reductions in 31% patients and cessation of therapy in 23% patients. Although the preliminary results of this study might demonstrate that imatinib has some potential activity, there are concerns regarding toxicity.

Bcl-2 inhibitor, G3139 (Oblimersen sodium; Genasense, Genta Inc., Berkeley Heights, NJ, USA)

Bcl-2 regulates apoptosis and resistance to chemotherapeutic agents (82). *In vitro* studies have shown that Bcl-2 is expressed in WM cells, and that downregulation of Bcl-2 and increased cytotoxicity in WM cells may be achieved with G3139 (83). A Phase I/II clinical trial of G3139 was conducted in patients with relapsed or relapsed/refractory WM showed favorable tolerability but minimal activity (84), but no further development apparently since 2005 in WM disease.

Anti-CD70 antibody, SGN-70 (Seattle Genetics Inc., Bothell, WA, USA)

A study demonstrated that WM tumor cells secrete soluble CD27, which is elevated in patients with WM vs. healthy donors, and might potentially serve as a faithful marker of WM disease. The SGN-70 humanized monoclonal antibody binds to CD70 (the receptor-ligand partner of CD27), and treatment of SCID-hu mice with established WM, using the SGN-70 antibody, blocked disease progression in 12/12 mice, whereas disease progressed in all five untreated mice (85). SGN-70 might therefore represent a therapeutic option in WM for the future.

TACI-Ig, Atacicept

TACI-Ig, Atacicept (ZymoGenetics, Seattle, WA, USA) contains a soluble receptor fusion protein comprised of the extracellular domain of TACI and the Fc portion of a human IgG binds to both APRIL (A Proliferation-Inducing Ligand) and BLYS (B-Lymphocyte Stimulator), members of the tumor necrosis factor family that promotes B-cell survival (86, 87). An open-label, dose-escalation phase 1b study enrolled 16 patients in 2006 with active progressive WM (88). A biological response was observed in 75% of the patients with WM, but with only disease stabilization.

Resveratrol

Resveratrol (Candlewood Stars Inc., Danbury, CT, USA) is a polyphenolic natural product, synthesized by a wide variety of plant species including grapes. It has gained considerable attention because of its anti-cancer properties, as demonstrated in solid and hematological malignancies (89). Resveratrol induced significant *in vitro* and *in vivo* effect in WM disease (90). A phase II clinical trial of resveratrol is under development.

Sildenafil citrate

Sildenafil citrate (Viagra®; Pfizer Pharmaceutical, Manchester, CT, USA) (91). Based on the clinical observation that patients receiving sildenafil citrate had a decrease in their IgM (92), a phase II trial of single agent sildenafil citrate in patients with slowly progressing WM was initiated. The purpose of the study was to delay time to progression in these patients. Thirty patients were treated on this study, and disease progression was suppressed in more than 50% of the patients. After 3 months of therapy, 17% showed a minor response. However, disease progression at 6 months of follow up occurred in almost all the patients. There is no further development apparently since 2007 in WM disease.

AMD3100 (Genzyme, Cambridge, MA, USA)

The normal process of B-cell homing is regulated by cytokines, chemokines, and adhesion molecules, including stromal derived factor SDF-1 and its receptor CXCR4. A recent study has shown that WM cells and patient samples highly express CXCR4; and SDF-1 induces migration and adhesion of WM cells (93). Adhesion of WM cells to stromal cells confers resistance to apoptosis and induces proliferation. The CXCR4 inhibitor AMD3100 inhibited migration and adhesion of WM cells to fibronectin, endothelial cells, and stromal cells. These studies provide the preclinical framework to study AMD3100 (a CXCR4 inhibitor) in WM for the future.

Triterpenoids, CDDO and CDDO-Im (Reata Pharmaceuticals Inc., Irving, TX, USA)

2-cyano-3, 12-dioxoolean-1,9-dien-28-oic acid (CDDO) and its methyl ester derivative (CDDO-Me) and imidazole derivative (CDDO-Im) are synthetic triterpenoids derived from oleanolic acid (94). *In vitro* studies in primary WM samples showed that CDDO-Im inhibited cell proliferation and induced apoptosis in WM cells compared to normal B cells. CDDO-Im induced may have potential efficacy in WM patients.

Simvastatin (HMG-CoA reductase inhibitor; Merck & Co., White House Station, NJ, USA)

In a cohort of 110 WM patients, WM patients receiving statin cholesterol-lowering drugs had significantly lower IgM levels vs. patients not on a statin drug (95). Simvastatin induced some dose-dependent inhibition of proliferation, cytotoxic effect and apoptosis in WM cells at a longer time-point as compared with other agents (95). Cholesterol-lowering agents may therefore have potential efficacy in patients with slowly progressing WM.

Conclusion

There have been significant advances in the understanding of the pathogenesis and molecular alterations that occur in WM. Based on these progresses, many targeted therapeutic agents and monoclonal antibodies have been tested in the preclinical setting and in early phase II studies. Clinical trials further establishing the optimal use of these agents, as monotherapy or in combined therapy as well as evaluation of several novel agents currently in preclinical studies are warranted. The current challenge is to identify combinations of agents that act synergistically against WM cells in order to carry out clinical trials that achieve high remission rates and prolonged survival in patients with WM.

Acknowledgement

The authors want to thank the researchers in the laboratory whose work is the cornerstone of the progress made in the understanding of Waldenström macroglobulinemia and in the development of targeted therapeutics: Abdel kareem Azab, Ph D, Judith Runnels, PhD, Xiaoying Jia, Hai T. Ngo, Feda Azab, Molly R Melhem, Antonio Sacco. This study was supported in part by International Waldenström macroglobulinemia Foundation (IWMF) grant, XL is a recipient of the Franco-American Fulbright Foundation.

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