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Waldenstrom Macroglobulinemia★

Xavier Leleu^{a,b}, Aldo M. Roccaro^{a,c}, Anne-Sophie Moreau^{a,b}, Sophie Dupire^b, Daniela Robu^b, Julie Gay^b, Evdoxia Hatjiharissi^a, Nicholas Burwik^a, and Irene M. Ghobrial^{a,*}

^a Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, 44 Binney Street, Boston, MA 02115, USA

^b Service des Maladies du Sang, Hopital Huriez, CHRU, Lille, France

^c Department of Internal Medicine and Oncology, University of Bari Medical School, Bari, Italy

Abstract

In the past years, new developments have occurred both in the understanding of the biology of Waldenstrom Macroglobulinemia (WM) and in therapeutic options for WM. WM is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy. Despite advances in therapy, WM remains incurable, with 5–6 years median overall survival of patients in symptomatic WM. Therapy is postponed for asymptomatic patients, and progressive anemia is the most common indication for initiation of treatment. The main therapeutic options include alkylating agents, nucleoside analogues, and rituximab. Studies involving combination chemotherapy are ongoing, and preliminary results are encouraging. No specific agent or regimen has been shown to be superior to another for treatment of 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 better target therapeutics for this malignancy. These efforts have led to the development of several novel agents including the proteasome inhibitor bortezomib, and several Akt/mTor inhibitors, perifosine and Rad001, and immunomodulatory agents such as thalidomide and lenalidomide. Studies with monoclonal antibodies are ongoing and promising including the use of alemtuzumab, SGN-70, and the APRIL/BLYS blocking protein TACI-Ig atacept. Other agents currently being tested in clinical trials include the PKC inhibitor enzastaurin, the natural product resveratrol, as well as the statin simvastatin. This report provides an update of the current preclinical studies and clinical efforts for the development of novel agents in the treatment of WM.

Keywords

Waldenstrom Macroglobulinemia; Novel therapy; Transplantation

1. Introduction

Waldenstrom 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 [1], first described by Dr. Jan

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* Corresponding author. Tel.: +1 617 632 4198; fax: +1 617 632 6624. Irene_ghobrial@dfci.harvard.edu (I.M. Ghobrial).

Gosta Waldenstrom 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 diagnosed per year in USA [2,3]. This incidence might be underestimated because many patients are misdiagnosed or not diagnosed early due to lack of symptoms at early stages of the disease. The median age varies between 63 and 68 years, with 55–70% men [4]. The incidence of WM is higher among whites, with blacks representing only 5% of all patients [5].

WM is believed to be predominantly a sporadic disease; however, studies have demonstrated a high familial incidence of this disease, with 18.7% of the patients having at least a first degree relative with a B-cell neoplasm [6,7]. Moreover, patients with a familial history of WM or a plasma cell disorder received the diagnosis at a younger age and with greater bone marrow involvement. The main risk factor for the development of WM is preexisting IgM-monoclonal gammopathy of undetermined significance (MGUS), which confers 46 times higher relative risk than for the general population [8]. Morra et al. [9] showed a progressive increase in the risk of transformation from asymptomatic IgM-MGUS to symptomatic WM, with increasing IgM levels. A possible association between hepatitis C virus and WM had been suggested [10], but this has been negated recently by Leleu et al. [11]. Reports of links between human herpes virus-8 and WM are unconfirmed.

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 [12,13]. The malignant cells have undergone VH gene somatic mutation, but not isotype class switching. Deletions in 6q21-22.1 were confirmed in most WM patients regardless of family history [14]. Analysis of 14q32 indicates the absence of Ig heavy chain (IgH) rearrangements in WM [15]. Many genes are thought to be dysregulated in WM, but further studies to define the role of these genes in the pathogenesis of WM are underway [16]. WM is characterized by upregulation of cytokines and chemokines that induce proliferation and survival of the malignant clone. These include B-lymphocyte stimulator (BLyS), IL-6, CD40 ligand, BAFF, APRIL, and stromal derived factor (SDF-1) [16–20].

2. Diagnostic criteria

WM is currently classified by the Revised European American Lymphoma (REAL) and World Health Organization (WHO) systems as a lymphoplasmacytic lymphoma [1,21]. The median age varies between 63 and 68 years, with 55–70% men [4]. WM cells express pan B-cell markers including CD19, CD20, and CD22, but lack CD10, CD23, CD38, FMC7, and cytoplasmic Ig [22]. CD5 and CD23 are expressed in 5–20% and 35% of the cases, respectively [23].

3. Signs and symptoms

WM is a heterogenous disease and patients can present with a broad spectrum of symptoms and signs [24,25]. 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 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 cytopenia. Patients may also present with symptoms of hyperviscosity related to elevate 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. Other presentation features include peripheral neuropathy, cryoglobulinemia, skin rash (Shnitzler's syndrome is the term for IgM monoclonal gammopathy associated with urticarial skin

lesions, fever, and arthralgia), cold-agglutinin hemolytic anemia, and amyloidosis. Anti-myelin-associated glycoprotein (MAG) antibody has been implicated in the demyelinating neuropathy found in WM [26].

4. Differential diagnostic

The presence of clonal B cells with lymphoplasmacytic differentiation in the bone marrow or a serum monoclonal IgM protein are not pathognomonic for WM and may be seen in other B-cell lymphoproliferative disorders including splenic marginal zone lymphoma (SMZL) [27,28]. SMZL can be distinguished from WM on the basis of immunophenotypic and molecular cytogenetic studies. Ocio et al. [29] demonstrated that CD22 and CD11c were overexpressed in patients with SMZL, whereas CD25 was more common in WM. The chromosomal abnormality most commonly in SMZL is the loss of 7q along with +3q and +5q [30]. Some patients may have detectable bone marrow clonal B cells but no morphologic evidence of bone marrow infiltration at trephine biopsy. These patients should be classified as having IgM-MGUS and monitored without therapeutic intervention [8]. Results from FISH studies indicate that 6q- has been suggested as a clinical marker to distinguish WM from IgM-MGUS [14]. When a patient presents with features typical of MM and an IgM component, a diagnosis of IgM-MM is made. The distinction between IgM-MM and WM is based on the pure plasma cell morphology in myeloma and presence of lytic bone lesions in myeloma [31]. B-cell chronic lymphocytic leukemia (CLL) may mimic WM clinically. Morphology and immunophenotyping are adequate to diagnose CLL. Lymphocytes are typically small and mature, without visible nucleoli, and smudge cells are characteristic [32]. The lymphocytes in CLL are positive for CD5 and CD23, whereas both are usually negative in WM. The presence of strong cytoplasmic immunoglobulin in WM also helps in making the distinction [21]. Patients with CLL frequently have IgM-MGUS [33].

5. Prognosis and initiation of therapy

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 years; however, a recent study in patients with symptomatic WM, demonstrated median disease specific survival of 11.2 years [34] (see Table 1).

Several studies have evaluated the effects of different clinical and laboratory variables on patient outcome [35]. Factors associated with poor prognosis in patients with WM include: advanced age, high β 2-microglobulin, cytopenias, low albumin, and organomegaly [34,36–38]. Age, hemoglobin concentration, serum albumin level, and β 2-microglobulin were identified as the predominant outcome predictors in these studies [34]. Because the serum IgM level does not reflect in a sensitive and accurate fashion the tumor burden or prognosis in WM, other markers of prognosis have been tested in several studies. An International Prognostic Scoring System (WM-IPSS) was presented at the 2006 American Society of Hematology panel as a staging system for survival for symptomatic patients in need of therapy [39] (Table 2). The parameters used to stratify risk were age older than 65 years, β 2-microglobulin level greater than 3 mg/L, monoclonal protein greater than 70 g/L, hemoglobin less than 11.5 g/dL, and platelet count less than $100 \times 10^9/L$. Low risk was defined as the presence of fewer than 1 adverse characteristic except age; high risk, as the presence of more than 2 adverse characteristics; the remaining patients with 2 adverse characteristics or older than 65 years had intermediate risk (Table 2). Other prognostic markers being considered in current studies are the serum free light chain and serum soluble and CD27 [40,41].

The Third International Workshops on WM confirmed the original recommendations of consensus panels on WM 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 [42]. The most common reason for initiation of therapy is anemia. Other causes include hyperviscosity symptoms, cytopenias, evidence of disease transformation and significant neuropathy, adenopathy or hepatosplenomegaly [42–44].

The evolution of WM to diffuse large B-cell lymphoma (DLBCL) as a result of histologic transformation has been described [45,46]. Onset of DLBCL is usually characterized by an aggressive clinical course and usually manifests as worsening constitutional symptoms, profound cytopenias, extramedullary disease, and organomegaly. The clinicopathologic features at diagnosis of WM do not predict the risk of DLBCL [45,46]. The outcome of this complication is controversial.

6. Therapeutic options

There is no standard of therapy and no FDA approved therapeutic agents for the specific treatment of WM [7]. Most treatment options were originally derived from other lymphoproliferative disease including Multiple Myeloma and CLL [43]. The Third International Workshop on MM updated the treatment recommendations for front-line and salvage therapy of WM [42].

The panel emphasized that many factors should be considered in making the decision: the age of the patient, presence of cytopenias, and the rate of disease progression. The new response criteria recommended in the Second International Workshop of WM are summarized in Table 3.

6.1. In frontline

The use of alkylator drugs (such as chlorambucil, cyclophosphamide, and melphalan), 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% in frontline. Notable, however, has been the lack of complete responses with the use of these agents or regimens in the frontline setting, with CR rates of 8–10% observed [42]. However, the panel recommended that for patients who may be eligible for autologous transplant, exposure to alkylator agents, and nucleoside analogues should be limited in view of reports suggesting depletion of stem cells by these agents [42,46].

Chlorambucil (0.1 mg/kg, Qid, oral) was the first agent used, with response rates varying between 31% and 92% [47]. The most common complication of therapy with alkylating agents is development of myelodysplasia and acute nonlymphocytic leukemia from therapy-induced chromosomal breakage [48]. Cladribine (0.1 mg/kg, for 5 to 7 days, IV) has shown response rates in the range of 44–90% [49,50]. Response rates to fludarabine (25–30 mg/m², 3 days, IV) as initial therapy range from 38% to 100% [51,52]. Fludarabine and cladribine are cross-resistant. The principal dose limiting toxicity of both these agents is bone marrow suppression and immunosuppression, predisposing patients to infections.

Response rates to rituximab (375 mg/m², 4 weekly injections IV) vary between 20% and 50% [53–55]. Rituximab may be regarded as a reasonable choice for treating patients with IgM autoantibody-related neuropathies [56]. Patients with polyneuropathy associated with anti-MAG antibodies treated with high-dose rituximab have shown clinical improvement as well as improvement of nerve conduction velocities and decreased anti-MAG antibody titers [57]. 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 [58]. Polymorphisms

in the FcγRIIIA (CD16) receptor gene may affect response to rituximab [59]. Transient increases in IgM titers 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, which may result in the loss of the therapeutic antibody [60,61]. Patients who had initial IgM flares had worse response rates compared to those with lower IgM levels (28% vs 80%). Some patients receive maintenance therapy with rituximab. Although the impact of this regimen on the time to progression has not been determined specifically in WM, it has prolonged time to progression in patients with other low-grade lymphomas who received rituximab maintenance compared to those who did not [62]. The use of radioimmunotherapy such as iodine 131I-tositumomab radioimmunotherapy 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 [63].

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 [42,56].

Several combinations including these agents have been studied (Table 4). The addition of alkylating agents to nucleoside analogues is active against WM. For example, the combination of oral cyclophosphamide with subcutaneous cladribine in 37 newly diagnosed patients achieved 84% PR or more, with a median duration of response of 36 months [64]. The combination of fludarabine and intravenous cyclophosphamide resulted in 55–78% overall response, with median time to treatment failure of 27 months [65]. Hematologic toxicity was commonly observed. A phase II clinical trial of 60 patients with WM treated with cyclophosphamide, rituximab and dexamethasone (DRC) demonstrated an overall response rate of 70%, with 7% complete remission [66]. Treatment was well tolerated and the main toxicity observed was grade 3–4 neutropenia in 20% of the patients. The combination of rituximab, cladribine and cyclophosphamide was tested in 17 previously untreated patients with WM and achieved at least a partial response in 94% of the patients, with complete response in 18% [42,64]. The combination of rituximab and fludarabine was evaluated in WM patients, with an overall response rate of 91% and CR of 7% [67]. In another study, the combination of fludarabine, cyclophosphamide and rituximab (FCR) was tested in WM patients with an overall response rate was 52%, with 5% complete remissions [42].

The combination of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) together with rituximab (CHOP-R) has been tested in patients with WM. The German Low-Grade Lymphoma Study Group (GLSG) performed a randomized upfront study of CHOP-R vs CHOP in 72 patients with low-grade lymphoma (71% of who had lymphoplasmacytic lymphoma). The response rate in the CHOP-R arm was 94% compared to 69% in the CHOP arm (Buske et al. unpublished). These results were confirmed in a small retrospective study of patients with relapsed WM [68]. A prospective study of CHOP-R in newly diagnosed patients with WM is ongoing in the Eastern Cooperative Oncology Group.

6.2. 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 [42–44].

High-dose chemotherapy with autologous stem cell rescue in primary refractory or relapsed disease should be considered for eligible patients. However, allogeneic and “nonmyeloablative 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 [42–44]. As such, the development of novel and stem cell sparing agents has been prioritized in the treatment of WM.

7. Novel therapeutics agents

7.1. Proteasome inhibitor

Proteasomal degradation is involved in physiological protein turnover and is the main mechanism accounting for intracellular protein degradation, such as signal transduction, cell cycle, and apoptosis. Proteasome inhibitors such as bortezomib have become the focus of clinical research in many malignancies including WM. The prototype 26S proteasome inhibitor bortezomib (Velcade, PS-341) selectively binds to the catalytic domain of the proteasome and prevents its activity [69,70]. Proteasome inhibitor bortezomib induces apoptosis of primary WM lymphoplasmacytic cells, as well as the BCWM.1 and WM-WSU WM cell lines at pharmacologically achievable levels. Based on its activity in MM, single agent bortezomib (1.3 mg/m², J1, 4, 8, 11; cycles 21 days, IV, 8 cycles) was tested in WM in phase II trials and achieved 40–80% responses [71–73]. As part of an NCI-Canada study, Chen et al. [72] treated 27 patients with both untreated (44%) and previously treated (56%) disease. Patients in this study received bortezomib utilizing the standard schedule until they either demonstrated progressive disease, or 2 cycles beyond a complete response or stable disease. The overall response rate in this study was 78%, with major responses observed in 44% of patients. Sensory neuropathy occurred in 20 patients, 5 with grade >3, and occurred following 2–4 cycles of therapy. Among the patients developing a neuropathy, 14 patients resolved and one patient demonstrated a one-grade improvement at 2–13 months. These results were confirmed in a multi-center study of the Waldenstrom Macroglobulinemia Clinical Trials Group (WMCTG) [73]. Responses were prompt, and occurred at median of 1.4 months. The median time to progression for all responding patients in this study was 7.9 (range 3–21.4+) months, and the most common grade III/IV toxicities occurring in >5% of patients were sensory neuropathies (22.2%), leukopenia (18.5%), neutropenia (14.8%), dizziness (11.1%), and thrombocytopenia (7.4%). Importantly, sensory neuropathies resolved or improved in nearly all patients following cessation of therapy. In addition to the above experiences with bortezomib monotherapy in WM, Dimopoulos et al. [71] observed major responses in 6 of 10 (60%) previously treated WM patients. 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 [73].

The addition of rituximab as well as steroids to bortezomib has been the subject of both preclinical as well as clinical investigation in various B-cell malignancies. In a trial by the WMCTG, bortezomib has been combined with dexamethasone and rituximab (BDR) for the primary therapy of patients with WM. The regimen proposed IV bortezomib at 1.3 mg/m² and IV dexamethasone 40 mg on days (1, 4, 8, and 11), and rituximab at 375 mg/m² (day 11). Patients received four consecutive cycles, followed by a three-month pause, and then 4 more cycles, each given three months apart. The development of peripheral neuropathy occurs in up to half of patients and are concerning using this schedule [74]. In addition, 4 of the first 7 patients receiving BDR in this study developed herpes zoster necessitating prophylaxis. In addition, Ghobrial et al. at the Dana-Farber Cancer Institute are examining the use of weekly intravenous bortezomib at 1.6 mg/m² along with rituximab (at 375 mg/m²) in patients with relapsed/refractory WM with an overall response rate of over 80% in

the first 17 evaluable patients (out ASH abstract). 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 WM.

7.2. The immunomodulatory agents (IMiDs)

In view of their success in the treatment of patients with Multiple Myeloma, IMiDs were tested in patients with WM, although their experience is limited. Thalidomide is nonmyelosuppressive, immunomodulatory, and antiangiogenic and may 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 [75]. 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 [76].

7.2.1. Thalidomide—A study to evaluate thalidomide alone showed partial response in 5 of 20 previously untreated and treated patients (25%) who received single agent thalidomide. Adverse effects were common and prevented dose escalation of thalidomide in 75% of patients [75]. However, a follow up study of 10 patients with higher doses of thalidomide (200 mg daily) showed only 20% overall response rate (Treon et al. unpublished). Thalidomide (50 mg daily) in combination with dexamethasone (40 mg orally once a week) and clarithromycin (250 mg orally twice a day) induced partial response in 10 of 12 (83%) previously treated patients [77].

In a previous study, the immunomodulators thalidomide significantly augmented rituximab mediated antibody dependent cell mediated cytotoxicity (ADCC) against lymphoplasmacytic cells [78]. Moreover, an expansion of natural killer cells has been shown to be associated with rituximab response. A phase II study of the combination of thalidomide and rituximab in 23 patients triggered response in 15 patients. No patients with stable disease or better have progressed with a median follow-up of 10 months (range 6–13 months) [79]. Intended therapy for patients on the phase II study of thalidomide plus rituximab consisted of thalidomide administered at 200 mg daily for 2 weeks, followed by 400 mg daily thereafter for one year. Patients received four weekly infusions of rituximab at 375 mg/m² beginning one week after initiation of thalidomide, followed by four additional weekly infusions of rituximab at 375 mg/m² beginning at week 13. Twenty three patients were evaluable in this study, overall and major response rates were of 78% and 70%, respectively. With a median follow-up of 42+ months, the median TTP for responders was 38+ months. Dose reduction of thalidomide occurred in all patients and led to discontinuation in 11 patients. Among 11 patients experiencing grade >2 neuroparesthesias, 10 demonstrated resolution to grade 1 ($n = 3$) or complete resolution ($n = 7$) at a median of 6.7 (range 0.4–22.5 months).

7.2.2. Lenalidomide—Similarly, based on the potent activity of lenalidomide in MM and the lack of neuropathy with this agent, a phase II study of lenalidomide 25 mg daily in combination with rituximab is ongoing in patients with relapsed or relapsed/refractory WM. Lenalidomide was administered for 3 weeks, followed by a one week pause for an intended duration of 48 weeks. Patients received one week of therapy with lenalidomide, after which rituximab (375 mg/m²) was administered weekly on weeks 2–5, then 13–16 [80]. Twelve patients were evaluable for an overall and a major response rate of 67% and 33%, and a median TTP of 15.6 months. Acute decreases in hematocrit were observed during first 2 weeks of lenalidomide therapy in 13/16 (81%) patients with a median hematocrit decrease of 4.4% (1.7–7.2%), resulting in hospitalization in 4 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. A phase I/II escalate dose single agent lenalidomide relapse/refractory WM clinical trial should open in 2008 in France in order to address the best tolerated dose.

7.3. Monoclonal antibodies and blocking proteins

7.3.1. Alemtuzumab—Alemtuzumab is a humanized monoclonal antibody which targets CD52, an antigen widely expressed on bone marrow LPC in WM patients, as well as on mast cells which are increased in the BM of patients with WM [81]. A phase II study of alemtuzumab was conducted in 25 patients with relapsed WM or newly diagnosed untreated [82]. Patients received 3 daily test doses of alemtuzumab (3, 10, and 30 mg IV) followed by 30 mg alemtuzumab IV three times a week for up to 12 weeks. All patients received acyclovir and bactrim or equivalent prophylaxis for the duration of therapy plus 8 weeks following the last infusion of alemtuzumab. All patients tolerated test dosing, and completed a median of 33 infusions (range 10–36) post test-dosing. WM patients showed an overall response rate of 76%, including 8 (32%) partial responses and 11 (44%) minor responses. Hematological toxicities were common among previously treated (but not untreated) patients and included grade 3/4 neutropenia (39%); thrombocytopenia (18%); anemia (7%). G3/4 non-hematological toxicity for all patients included dermatitis (11%); fatigue (7%); and infection (7%). Cytomegalovirus (CMV) reactivation and infection was commonly seen among previously treated patients. Three patients died due to therapy-related complications. With a median follow-up of 8.5+ months, 11/19 responding patients remain free of progression. High rates of response with the use of alemtuzumab as salvage therapy have also been reported by Owen et al. [83], but opportunistic infections were common in this heavily pretreated population.

TACI-Ig, *atacept* (ZymoGenetics) 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 [84,85]. An open-label, dose-escalation phase 1b study enrolled 16 patients with refractory or relapsed MM or active progressive WM [86]. Sequential cohorts received one cycle of 5 weekly subcutaneous injections of atacept at 2, 4, 7 or 10 mg/kg. A total of 16 patients (12 MM and 4 WM) entered the trial, treatment with atacept was well tolerated, and no dose limiting toxicity was observed. A biological response was observed in this heavily treated refractory population, with disease stabilization in 75% of the patients with WM.

8. Signaling pathways inhibitors

8.1. Perifosine

Perifosine (KRX-0401, Keryx Biopharmaceuticals, NY) is a novel Akt inhibitor that belongs to a class of lipid-related compounds called alkylphospholipids [87]. It has shown activity in phase II trials in MM. Our previous studies have shown that the activity of the survival protein Akt is upregulated in patients with WM compared to normal B cells, and that downregulation of Akt leads to significant inhibition of proliferation and induction of apoptosis in WM cells in vitro [88]. These results were confirmed in vivo in a xenograft mouse model where perifosine have shown significant cytotoxicity and inhibition of tumor growth [88]. Based on this preclinical activity, a phase II trial of single agent perifosine in patients with relapsed or relapsed/refractory disease was initiated using 150 mg oral daily dosing [89]. Thirty seven patients were enrolled on the study and of the first 27 evaluable patients, the overall response rate was 31%. These preliminary results indicate that

perifosine is a well tolerated and promising agent to be used in combination in future studies in WM.

8.2. RAD001

Based on the preclinical data showing increased activity of the PI3K/mTOR pathway in WM [20,90], rapamycin (mTOR inhibitor) has been studied in vitro in WM and showed cytotoxicity in WM cell lines [91]. A phase II trial of single agent RAD001 (orally at 10 mg daily) was initiated in patients with relapsed or refractory WM. To date, 25 patients have been enrolled with an overall response rate of 40%, indicating promising activity for further evaluation of this agent in WM.

8.2.1. Bcl-2 inhibitor, G3139 (Oblimersen sodium; Genasense, Genta Inc, Berkeley Heights, NJ)—Bcl-2 regulates apoptosis and resistance to chemotherapeutic agents; it has therefore become an attractive target for anticancer therapy in a number of malignancies including WM [92]. 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 [93]. A phase I/II clinical trial of G3139 was conducted in patients with relapsed or relapsed/refractory WM showed favorable tolerability but minimal activity [94].

8.2.2. Imatinib mesylate (Gleevec)—Imatinib targets the microenvironment of WM through inhibition of stem cell factor signaling through CD117, which is expressed on WM tumor cells [95]. A phase II trial of single agent imatinib as performed in patients with relapsed or refractory WM [96]. Imatinib was given at 400 mg daily, with dose escalation to 600 mg after one month of therapy, for up to 2 years. After 3 months of therapy, 6/13 (46.2%) of patients achieved MR. 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. The preliminary results of this study therefore demonstrate that imatinib mesylate has potential activity, but there are concerns regarding toxicity.

9. Conclusion

In summary, there have been significant advances in the understanding of the pathogenesis and molecular alterations that occur in WM. Many targeted therapeutic agents and monoclonal antibodies have been tested in the preclinical setting and in early phase II studies. A new paradigm shift has evolved in WM utilizing novel therapeutic agents targeting the WM clone and its bone marrow microenvironment. 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.

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Table 1

Diagnostic criteria for Waldenstrom Macroglobulinemia [1]

-
- IgM monoclonal gammopathy of any concentration
 - Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation of any percentage (Determination by bone marrow biopsy)
 - Intertrabecular pattern of bone marrow infiltration
 - Surface IgM+ CD5 ± CD10 – CD19 + CD20 + CD22 + CD23 – CD25 + CD27 + FMC7 + CD103– CD138–. Variations from this phenotypic profile can occur
-

Table 2

International Prognostic Scoring System (WM-IPSS) [39]

	Low risk	Intermediate risk	High risk	
Age > 65 years	–	+		
		or		
Hb ≤ 11.5 g/dL	} ≤ 1 factor	} 2 factors	} >2 factors	
Platelet ≤ 100 × 10 ⁹ /L				
b2m > 3 mg/L				
IgM > 70 g/L				
N (%)	158 (27%)	223 (38%)	206 (35%)	
Survival at 5 years	87%	68%	36%	<i>P</i> < 0.001
Hb, hemoglobin; b2m, β2-microglobulin; N, number of patients; %, percentage.				

Table 3

Response criteria recommended by the Second International Workshop of WM [97]

Complete response (CR)	Disappearance of monoclonal protein by immunofixation; no histologic evidence of BM involvement, resolution of any adenopathy/organomegaly. Reconfirmation of CR is required after 6 weeks
Partial response (PR)	At least 50% reduction of serum monoclonal IgM concentration on protein electrophoresis and at least 50% decrease in adenopathy/organomegaly
Minor response (MR)	At least 25% reduction of serum monoclonal IgM by protein electrophoresis
Stable disease (SD)	Less-than-25% reduction in serum monoclonal IgM by electrophoresis
Progressive disease (PD)	At least 25% increase in serum monoclonal IgM by protein electrophoresis. Reconfirmation by a second measurement is required after 3 weeks

Table 4

Combination therapies in WM

Study	Regimen	No. of patients	Phase of study	ORR %
Tam [98]	Fludara/CTX	9	II	88
Tamburini [65]	Fludara/CTX	49	II	78
Weber [64]	Cladribine/CTX	37	II	84
Leblond [99]	Fludarabine vs CAP	92	III	30 vs 11%
Owen [1]	Fludara/rituximab	43	II	82
Tam [100]	Fludara/CTX/rituximab	5	II	80
Weber [101]	Cladribine/CTX/rituximab	27	II	94
Hensel [102]	Pentostatin/CTX/rituximab	17	II	90
Dimopoulos [66]	Dex/CTX/rituximab	72	II	83
Treon [68]	CHOP/rituximab	13	II	77
Dimopoulos [103]	CHOP/rituximab vs CHOP	72	II	94