Published in final edited form as:

Drugs Future. 2010 January ; 35(1): 53–58. doi:10.1358/dof.2010.35.1.1410182.

New Therapeutic Approaches for Waldenstrom Macroglobulinemia

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Abstract

Waldenstrom Macroglobulinemia (WM) is a B-cell disorder characterized by the infiltration of the bone marrow (BM) with lymphoplasmacytic cells, as well as detection of an IgM monoclonal gammopathy in the serum. WM is an incurable disease, with an overall median survival of only 5-6 years. First-line therapy of WM has been based on single-agent or combination therapy with alkylator agents (e.g. chlorambucil or cyclophosphamide), nucleoside analogues (cladribine or fludarabine), and the monoclonal antibody rituximab. Novel therapeutic agents that have demonstrated efficacy in WM include thalidomide, lenalidomide, bortezomib, everolimus, Atacicept, and perifosine. The range of the ORR to these agents is between 25-80%. Ongoing and planned future clinical trials include those using PKC inhibitors such as enzastaurin, new proteasome inhibitors such as carfilzomib, histone deacetylase inhibitors such as panobinostat, humanized CD20 antibodies such as Ofatumumab, and additional alkylating agents such as bendamustine. These agents, when compared to traditional chemotherapeutic agents, may lead in the future to higher responses, longer remissions and better quality of life for patients with WM.

Introduction

Waldenstrom Macroglobulinemia (WM) is a B-cell disorder characterized by the infiltration of the bone marrow (BM) with lymphoplasmacytic cells, as well as demonstration of an IgM monoclonal gammopathy¹⁻⁴ WM is classified, according to the Revised European American Lymphoma (REAL) and World Health Organization (WHO) systems, as a lymphoplasmacytic lymphoma^{3,4}. The overall incidence of WM is about 3 per million persons per year, which includes 1,500 new cases diagnosed each year in the United States^{7,5,6}. The incidence rates are higher in Caucasians compared with African-Americans and when looking at the age-adjusted rates for men and women within the US, men have a higher incidence with 3.4 per million compared to 1.7 per million^{5,7}. The most recognized risk factor for developing WM is IgM-monoclonal gammopathy of undetermined significance (IgM-MGUS), which confers a 46 fold higher relative risk than the general population¹⁰. There is also a higher risk among individuals who have a first degree relative with a B- cell neoplasm; which is about 18.7% of patients in various studies^{8,9}. WM remains an incurable disease with an overall median survival of only 5-6 years and a median disease specific survival of 11.2 years⁷. Factors associated with poor prognosis include advanced age, high β 2-microglobulin (β 2M), cytopenias, low albumin, serum IgM monoclonal protein, and organomegaly⁷⁻¹¹. Based on a series of 587 patients, an international prognostic scoring system (ISS-WM) was recently presented, table 1. This prognostic model was based on 5 risk factors, age, β 2M, anemia, thrombocytopenia and serum IgM monoclonal protein

(Table 1). Patients with low risk disease had a 5-year survival of 87%, while patients with high-risk disease had a 5-year survival of only 36%. This is now accepted as the uniform prognostic staging system for WM¹².

Clinical manifestations

The signs and symptoms of WM may vary, but are usually related to signs of marrow infiltration such as anemia or cytopenias, or symptoms and signs of hyperviscosity due to the elevated IgM level in the serum^{2,3,11}, and hepatosplenomegaly and lymphadenopathy may occur in about 20% of WM patients. Other symptoms may include B symptoms, consisting of fever, night sweats, and weight loss, or rare symptoms and signs of the disease such as cryoglobulinemia, skin rash (Schnitzler syndrome), raynaud's disease, amyloidosis and CNS involvement (Bing-Neel syndrome)¹³⁻¹⁵.

When and how to treat

Patients with WM should be treated based on the presence of symptoms or signs of disease progression. Patients who are asymptomatic should not be treated independent of the monoclonal protein level. Frequently, physical manifestations contributing to the need to initiate therapy include: platelet count $<100 \times 10^9/L$, hemoglobin level <10 g/dL, symptomatic hyperviscosity, amyloidosis, bulky adenopathy or organomegaly, severe or advancing peripheral neuropathy, cryoglobulinemia, or cold-agglutinin disease^{15,16}. Determining the most appropriate route of therapy, once established as necessary, should take into account the patient's age, occurrence of cytopenias, requirement of rapid disease control, as well as the patient's eligibility for autologous transplant therapy¹⁶.

Therapeutic options

Standard therapeutic options

First-line therapy of WM has been based on single-agent therapy with alkylator agents (e.g. chlorambucil or cyclophosphamide), nucleoside analogues (cladribine or fludarabine), and the monoclonal antibody rituximab¹⁷⁻²⁰. Response is assessed by the consensus panel recommendations of the second international workshop for WM^{16,21,22}, Table 2. These agents have overall response rates (ORR) in the upfront setting ranging from 30-70%; this includes complete response (CR), partial response (PR), and minimal response (MR), with CR rates $< 10\%$, and median durations of response averaging 2-3 years^{18,23}. In the salvage setting, the ORR is between 30-40%, with a median response duration ≤ 1 year^{18,24}.

Fludarabine in combination therapy is another common treatment option. This therapeutic option is known to stimulate high responses; however significant toxicities are often a problem for these elderly patients^{25,26}. It can also lead to long-term remissions. A recent update of the Southwest Oncology Group-directed Intergroup Trial S9003 showed that the 10-year event-free survival to single-agent fludarabine was 20%. Unfortunately, it has been found that these agents can increase the development of myelodysplasia or acute myelogenous leukemia, and has been associated with increased disease transformation risk, and therefore should be used judiciously with WM patients²⁷.

The use of cyclophosphamide-containing regimens has also shown significant responses in patients with WM^{3,28,29}. Dimopoulos et al²⁹ has shown that the combination of rituximab, cyclophosphamide, and dexamethasone (R-CD) led to overall and complete responses in 78% and 7% of WM patients, respectively, and a 2-year progression-free survival of 80%. These results are comparable to those observed with cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (CHOP-R)³⁰, indicating that the addition of vincristine and doxorubicin in patients with WM may not be necessary.

The most commonly used therapeutic agent in WM is rituximab. Standard treatment involves 4 weekly infusions of 375 mg/m² or extended treatment involving 4 weekly rituximab treatments repeated at 3 months. This treatment regime has yielded response rates of 35-48%^{19,31-33}. Rituximab has been found, in about 54% of patients, to cause IgM flare, which is an initial increase in the IgM level lasting up to 3 – 4 months^{34,35}. These elevated IgM levels do not indicate treatment failure.

A viable treatment option that could be employed, when feasible for patients, is autologous transplant therapy. The European Bone Marrow Transplant Registry recently reported the largest experience for both autologous stem cell transplant (SCT) as well as allogeneic stem cell transplant in WM³⁶. They reported data on 202 WM patients who mostly had relapsed or refractory disease. Using autologous stem cell transplant, the 5-year progression-free and overall survival rates were 33% and 61%, respectively. The data for allogeneic transplant showed that in 44 heavily pretreated patients with WM who received a conventional myeloablative allogeneic SCT and 62 patients who received reduced-intensity conditioning (RIC) allogeneic SCT, the 3-year non-relapse mortality rate for all patients was 33%, and the 5-year progression-free and overall survival rates were 48% and 63%, respectively³⁶. Patients who are eligible for autologous SCT should not be exposed to specific therapies, which include alkylating agents or nucleoside analogues. These are to be avoided as a study recently found that treatment with these agents has led to difficulty collecting stem cells¹⁹.

Novel therapeutic agents

Novel therapeutic agents that have demonstrated efficacy in WM in clinical trials include thalidomide, lenalidomide, bortezomib, everolimus, Atacicept, and perifosine^{18,37-39}, see Table 3. The range of the ORR to these agents is between 25-80%^{18,37-39}. Ongoing clinical trials include those with Ofatumumab, enzastaurin, LBH589 (panobinostat), and Carfilzomib⁴⁰ (ClinicalTrials.gov). In addition, multiple other novel therapeutic agents are currently being tested in the preclinical setting. These include MDX-1097, PR-047, BEZ-235, PKC412, AZD0635 and TKI-258⁴¹⁻⁴³.

Thalidomide has shown efficacy in WM either alone or in combination with rituximab. The combination of thalidomide and rituximab using thalidomide 200 mg daily for the first 2 weeks followed by 400 mg daily for a total of one year was tested in 23 patients with WM. The ORR was 78% with 65% partial responses. However, dose reductions were necessary in all of the patients due to neuropathy from thalidomide. This also led to discontinuation of therapy in 11 patients⁴⁴.

Based on the activity of lenalidomide in multiple myeloma, this agent was tested in combination with rituximab at 25 mg/day. In this phase II trial, only 16 patients were treated and the trial was stopped early due to toxicity. Acute decreases in hematocrit were observed during the first 2 weeks of lenalidomide therapy in 13/16 (81%) patients with a median hematocrit decrease of 4.4% (1.7-7.2%)⁴⁵. The overall response rate on this study was 67% in 12 evaluable patients with 4 partial responses. Ongoing phase I studies of escalating doses of lenalidomide should help define the role of this agent in this disease.

Bortezomib has been tested in 2 phase II clinical trials as a single agent in relapsed WM. The agent was used in the standard dose of 1.3 mg/m² twice a week on days 1, 4, 8 and 11. The first study was performed by Chen et al⁴⁶ in 27 patients with untreated or previously treated WM. The ORR was 78% and major responses (PR or better) were seen in 44% of patients. The main toxicity was sensory neuropathy that was observed in 20 patients. More recently, the combination of bortezomib, rituximab and dexamethasone (BDR) was tested in newly diagnosed patients with WM and showed an overall response rate of 96% including 83% PR⁴⁷. Given that neuropathy is a major toxicity in patients receiving standard treatment

schedules of bortezomib, we and others have developed studies using bortezomib once a week at 1.6 mg/m² in an attempt to reduce the occurrence of peripheral neuropathy⁴⁷. Several clinical trials are ongoing using weekly bortezomib in combination with rituximab in newly diagnosed or in relapsed WM^{48,49}. The results of the study using weekly bortezomib and rituximab without the addition of dexamethasone in patients with relapsed WM has been recently presented⁴⁸. All patients received bortezomib IV weekly at 1.6 mg/m² on days 1, 8, 15, q 28 days × 6 cycles, and rituximab 375 mg/m² weekly on cycles 1 and 4. Thirty-seven patients were treated. At least minimal response (MR) or better was observed in 81% (95% CI: [65,92]) with 2 patients (5%) in complete remission (CR)/near CR, 17 (46%) in partial response (PR), and 11(30%) in MR. Similarly, the data of the same study in upfront untreated WM was presented in the American Society of Hematology meeting 2009⁴⁹. Twenty-six patients were treated. At least minimal response or better was observed using serum protein electrophoresis in 24/26 (92%) with 2 patients (8%) in complete remission (CR)/near CR, 15 (58%) in partial response (PR), and 7 (27%) in minimal response (MR). Two patients (8%) had stable disease. By using IgM by nephelometry, all 26 patients (100%) had at least a minor response, with 2 (8%) CR, 15 (58%) PR and 9 (35%) patients with minor response⁴⁹.

Most recently, the mTOR inhibitor everolimus (RAD001) was studied in a phase II clinical trial of 50 patients using everolimus 10 mg PO daily¹⁶ (Ghobrial et al, JCO, in press). The ORR was 70%, with 42% PR, and the estimated progression free survival (PFS) at 6 and 12 months was 75% and 62%, respectively. The most common grade 3 or 4 toxicities were anemia (18%), thrombocytopenia (16%), neutropenia (14%), diarrhea (6%), fatigue (10%), and stomatitis (8%).

Similarly, a phase II clinical trial using the Akt inhibitor Perifosine was studied in 37 patients (Ghobrial et al, CCR, in press). In this study, the ORR was 35%, with 4 patients achieving PR (11%). The median progression-free survival was 12.6 months. Perifosine was generally well tolerated; adverse events related to therapy were cytopenias (grade 3-4, 13%), gastrointestinal symptoms (grade 1-2, 81%), and arthritis flare (all grades, 11%)¹⁵.

A phase I study of Atacicept, a fusion protein that binds to and neutralises the B-cell survival factors, B-lymphocyte stimulator (BLyS) and A proliferation-inducing ligand (APRIL) was conducted in patients with multiple myeloma (MM) and WM⁵⁰. In this study, 16 patients with advanced disease (12 MM, 4 WM) received one cycle of five once-weekly subcutaneous injections of atacicept. Patients with stable disease after cycle 1 entered an extension study. Atacicept was well tolerated. Of four patients with WM, three patients were progression-free after cycle 1.

Bendamustine was recently tested in combination with rituximab (BR) in 42 patients with untreated WM^{16,51,52}. Encouragingly, BR had an ORR of 96% and had lower incidences of grade 3 and 4 cytopenias, infectious complications and alopecia when compared to a standard treatment of R-CHOP.

Future Direction of Novel therapeutic agents

Ongoing and planned future clinical trials include those using PKC inhibitors such as enzastaurin, new proteasome inhibitors such as carfilzomib, histone deacetylase inhibitors such as panobinostat and Ofatumumab.

Enzastaurin is a selective PKC inhibitor that showed significant in vitro and in vivo cytotoxicity in WM cell lines and patient samples⁵³. A phase II study is ongoing that is testing this agent in patients with relapsed or refractory WM⁴⁰. Carfilzomib is a selective inhibitor of the chymotrypsin-like activity of the immunoproteasome and constitutive

proteasome. Preclinical studies are ongoing with a plan to start phase II clinical trials in WM in the future. Similarly, panobinostat (LBH589) and other histone deacetylase inhibitors have been tested in the preclinical setting in WM and a phase II clinical trial of LBH589 has been initiated in patients with relapsed or refractory WM. Finally, the new humanized anti-CD20 antibody (Ofatumumab) is currently being tested in patients with relapsed WM. Given the tolerability and efficacy of ofatumumab in follicular lymphoma and Chronic Lymphocytic Leukemia, and the need to improve therapy for patients with WM especially with the side effects observed with rituximab, the phase II trial of ofatumumab may lead the way to change monoclonal therapeutic options in patients with WM. In addition, multiple other novel therapeutic agents are currently being tested in the preclinical setting. These include MDX-1097, PR-047, BEZ-235, PKC412, AZD0635 and TKI-258⁴¹⁻⁴³.

Conclusion

There has been a momentous shift in the understanding of WM and mechanistic ways to manipulate the WM cells. These new therapeutic agents have revolutionized the options for patients with WM. Future combinations of these agents should increase overall response rates with decreased toxicities. These agents, when compared to traditional chemotherapeutic agents, may lead in the future to higher responses, longer remissions and better quality of life for patients with WM.

Acknowledgments

Supported in part by the Kirsch lab for Waldenstrom and the Heje Fellowship for WM.

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Table 1

International Prognostic Scoring System (WM-IPSS)

Based on 5 Risk factors *	Low	Intermediate	High
	≤ 1 factor	2 factors or Age >65	>2 factors
N (%)	158 (27)	223 (38)	206 (35)
Survival at 5 years	87%	68%	36%

* 5 risk factors: age >65 years, hemoglobin ≤ 11.5 g/dL, platelet count $\leq 100 \times 10^9$ /L, beta2-microglobulin >3 mg/L and serum monoclonal protein concentration >7.0 g/dL.

Table 2

Response criteria recommended by the Second International Workshop of WM

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 3

Novel Therapeutic Agents

Study	Regimen	N	Phase	ORR
Chen ⁴⁶	Bortezomib	27	II	78%
Treon ³⁹	Bortezomib	26	II	84%
Treon ⁴⁷	bortezomib + Dex+ Rituximab (upfront)	23	II	96%
Treon ⁴⁴	Thalidomide + Rituximab	23	II	78%
Treon ⁴⁵	Lenalidomide + Rituximab	16	II	67%
Ghobrial ^{**}	Everolimus	50	II	70%
Ghobrial ^{**}	Perifosine	37	II	35%
Ghobrial ⁴⁸	Bortezomib weekly+rituximab (relapsed)	37	II	81%
Ghobrial ⁴⁹	Bortezomib weekly+rituximab (upfront)	37	II	92%
Rummel ⁵²	Bendamustine+ rituximab (upfront)	42	II	96%
Rossi ⁵⁰	Atacicept	4	I	NR

NR: not reported.

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In press.