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NEW THERAPEUTIC APPROACHES FOR WALDENSTRÖM'S MACROGLOBULINEMIA

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SUMMARY

Waldenström's macroglobulinemia (WM) is a B-cell disorder characterized by the infiltration of the bone marrow with lymphoplasmacytic cells, as well as detection of an immunoglobulin M (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 alkylating agents (e.g., chlorambucil or cyclophosphamide), nucleoside analogues (cladribine or fludarabine phosphate) 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 overall response rate to these agents is 25-80%. Ongoing and planned clinical trials include those using protein kinase C (PKC) inhibitors such as enzastaurin hydrochloride, 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 hydrochloride. In comparison with traditional chemotherapeutic agents, these agents may in the future lead to greater responses, longer remissions and better quality of life for patients with WM.

INTRODUCTION

Waldenström's macroglobulinemia (WM) is a B-cell disorder characterized by the infiltration of the bone marrow with lymphoplasmacytic cells, as well as demonstration of an immunoglobulin M (IgM) monoclonal gammopathy (1-4). According to the Revised European American Lymphoma system and the World Health Organization, WM is classified as a lymphoplasmacytic lymphoma (3, 4). The overall incidence of the disease is about 3 per million persons per year, which includes 1,500 new cases diagnosed each year in the United States. The incidence rates are higher in Caucasians than in African–Americans, and when looking at the age-adjusted rates for men and women within the U.S., men have a higher incidence than women (incidence of 3.4 per million and 1.7 per million, respectively) (5-7). The most recognized risk factor for developing WM is IgM monoclonal gammopathy of undetermined significance, which confers a 46-fold higher relative risk for WM compared with the general population (8). Individuals who have a first-degree relative with a B-cell neoplasm are also at higher risk for developing the disease, namely ~18.7% of patients in various studies (9, 10).

WM remains an incurable disease with an overall median survival of only 5-6 years and a median disease-specific survival of 11.2 years (7). Factors associated with poor prognosis include advanced age, high β_2-microglobulin, cytopenias, low albumin, serum IgM monoclonal protein and organomegaly (7-11). A total of 587 WM patients were recently analyzed to create an international prognostic scoring system (WM-IPSS), based on 5 risk factors: age, β_2-microglobulin, anemia, thrombocytopenia and serum IgM monoclonal protein (Table I). Among the patients with low-risk disease, 87% had a 5-year survival, while this value was only 36% in individuals with high-risk disease. The WM-IPSS is now accepted as the uniform prognostic staging system for WM (12).

CLINICAL MANIFESTATIONS

The signs and symptoms of WM may vary, but are usually related to signs of bone marrow infiltration (e.g., anemia or cytopenias) or to symptoms and signs of hyperviscosity caused by the elevated IgM level in the serum (2, 3, 11). In addition, hepatosplenomegaly and lymphadenopathy occur in about 20% of WM patients. Other possible symptoms include B symptoms (i.e., fever, night sweats and weight loss) or rare symptoms and signs (e.g., cryoglobulinemia and skin rash or Schnitzler's syndrome), Raynaud's disease, amyloidosis and involvement of the central nervous system (Bing–Neel syndrome) (13-15).

WHEN AND HOW TO TREAT

Individuals with WM should be treated based on the presence of signs or symptoms of disease progression. Patients who are asymp-

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Table I. *International Prognostic Scoring System for WM (WM-IPSS).*

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

*Age > 65 years, hemoglobin ≤ 11.5 g/dL, platelet count ≤ 100 × 10^9/L, β_2-microglobulin > 3 mg/L and serum monoclonal protein concentration > 7.0 g/dL.

tomatic should not be treated, independent of the monoclonal protein level. Frequently, physical manifestations contributing to the need to initiate therapy include a platelet count below 100 × 10^9/L, a hemoglobin level below 10 g/dL, symptomatic hyperviscosity, amyloidosis, bulky adenopathy or organomegaly, severe or advancing peripheral neuropathy, cryoglobulinemia and cold agglutinin disease (15, 16). Determining the most appropriate route of therapy, once established as necessary, should take into account the patient's age, the occurrence of cytopenias, the requirement for rapid disease control, as well as the affected individual's eligibility for autologous transplant therapy (16).

THERAPEUTIC OPTIONS

Standard therapeutic options

First-line therapy of WM has been based on single-agent therapy with alkylating agents (e.g., chlorambucil or cyclophosphamide), nucleoside analogues (cladribine or fludarabine phosphate) and the monoclonal antibody rituximab (17-20). Response is assessed by the consensus panel recommendations set at the Second International Workshop on WM (16, 21, 22), listed in Table II. The median duration of response to the agents used for first-line WM therapy is 2-3 years and these compounds produce overall response rates of 30-70% in that setting, which includes complete response rates of < 10%, partial response and minimal response (18, 23). In the salvage setting, the overall response rates fall between 30% and 40%, with a median response duration of ≤ 1 year (18, 24).

Fludarabine in combination therapy is another common treatment option and is known to stimulate high responses, although significant toxicities are often a problem in 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 with single-agent fludarabine was 20%. Unfortunately, as nucleoside analogues have been found to increase the development of myelodysplasia or acute myelogenous leukemia and have been associated with an increased risk for disease transformation, they should be used judiciously in WM patients (27).

Cyclophosphamide-containing regimens have also produced significant responses in patients with WM (3, 28, 29). Dimopoulos et al. (29) showed that the combination of rituximab, cyclophosphamide and dexamethasone led to overall and complete responses in 78% and 7%, respectively, of WM patients and a 2-year progression-free survival of 80%. These results are comparable to those observed with the combination of cyclophosphamide, doxorubicin, vincristine sulfate, prednisone and rituximab (30), indicating that the addition of vincristine and doxorubicin to WM therapy may not be necessary.

The most commonly used therapeutic agent for WM is rituximab. Standard treatment involves four weekly infusions of 375 mg/m^2 or extended treatment involving four weekly rituximab treatments repeated at 3 months. This treatment regimen has yielded response rates of 35-48% (19, 31-33). In about 54% of patients, rituximab has been found 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 in both autologous stem cell transplants and allogeneic stem cell transplants for WM. They reported data from 202 WM patients who mostly had relapsed or refractory disease. After autologous stem cell transplants, the 5-year progression-free and overall survival rates were 33% and 61%, respectively. In 44 heavily pretreated WM patients who underwent a conventional myeloablative allogeneic stem cell transplant and 62 patients who received a reduced-intensity conditioning allogeneic stem cell transplant, the 3-year nonrelapse mortality rate for all patients was 33% and the 5-year progression-free and overall survival rates were 48% and 63%, respectively (36). Patients who are eligible for an autologous stem cell transplant should not be exposed to specific therapies, including alkylating agents or nucleoside analogues, as a recent study found

Table II. *Response criteria recommended at the Second International Workshop on WM.*

Complete response	Disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement; resolution of any adenopathy/organomegaly; reconfirmation of complete response is required after 6 weeks
Partial response	A ≥ 50% reduction of serum monoclonal IgM concentration on protein electrophoresis and a ≥ 50% decrease in adenopathy/organomegaly
Minor response	A ≥ 25% reduction of serum monoclonal IgM by protein electrophoresis
Stable disease	A < 25% reduction in serum monoclonal IgM by electrophoresis
Progressive disease	A ≥ 25% increase in serum monoclonal IgM by protein electrophoresis; reconfirmation by a second measurement is required after 3 weeks

that treatment with these compounds has led to difficulty collecting stem cells (19).

Novel therapeutic agents

Novel therapeutic agents that have demonstrated efficacy in WM in clinical trials include thalidomide, lenalidomide, bortezomib, everolimus, atacicept and perifosine (Table III). The range of the overall response rates to these agents is 25-80% (18, 37-39). Ongoing clinical trials include those of ofatumumab, enzastaurin hydrochloride, panobinostat and carfilzomib (40). In addition, multiple other novel therapeutic agents are currently being tested in the preclinical setting, e.g., MDX-1097, PR-047, BEZ-235, midostaurin (PKC-412), AZD-0635 and dovitinib lactate (TKI-258) (41-43).

Thalidomide has shown efficacy in WM either alone or in combination with rituximab. The combination of thalidomide and rituximab was tested in 23 WM patients, using thalidomide 200 mg daily for the first 2 weeks followed by 400 mg daily for a total of 1 year. The overall response rate was 78%, with 65% partial responses. However, dose reductions were necessary in all patients due to neuropathy caused by thalidomide, which also led to discontinuation of therapy by 11 patients (44).

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 of the treatment. Acute decreases in hematocrit were observed during the first 2 weeks of lenalidomide therapy in 13 of 16 (81%) patients, with a median hematocrit decrease of 4.4% (1.7-7.2%) (45). The overall response rate was 67% in 12 evaluable patients, with 4 partial responses. Ongoing ascending-dose phase I studies of lenalidomide should help define the role of this agent in this disease.

Bortezomib has been tested in two phase II trials as a single agent in relapsed WM. The agent was used at the standard dose of 1.3 mg/m^2 twice weekly on days 1, 4, 8 and 11. The first study was performed by Chen et al. (46) in 27 patients with untreated or previously treated WM. The overall response rate was 78% and major responses (partial response or better) were seen in 44% of patients. The main toxicity was sensory neuropathy and was observed in 20 patients. More recently, the combination of bortezomib, rituximab and dexamethasone was tested in newly diagnosed WM patients and showed an overall response rate of 96%, including 83% partial responses. Given that neuropathy is a major toxicity in patients receiving standard treatment schedules of bortezomib, we and others have developed studies using bortezomib once weekly at 1.6 mg/m^2 in an attempt to reduce the occurrence of peripheral neuropathy (47).

Several clinical trials are ongoing of weekly bortezomib in combination with rituximab in newly diagnosed or relapsed WM patients (48, 49). The results of a study of weekly bortezomib and rituximab without the addition of dexamethasone in patients with relapsed WM were recently presented (48). All patients received weekly i.v. bortezomib 1.6 mg/m^2 on days 1, 8 and 15 every 28 days for 6 cycles, in addition to weekly rituximab 375 mg/m^2 during cycles 1 and 4. Among the 37 patients who were treated, a minimal response or better was observed in 81% (95% confidence interval [CI]: 65-92), with 2 patients (5%) in or near complete remission, 17 (46%) partially responding and 11 (30%) showing a minimal response. Data from the same study in untreated WM were presented at the American Society of Hematology meeting in 2009. Using serum protein electrophoresis, a minimal response or better was observed in 24 (92%) of the 26 treated patients, with 2 individuals (8%) in or near complete remission and 15 (58%) showing partial response. Employing the same method, minimal response was observed in 7 (27%) of the participants and 2 patients (8%) had stable disease. Using nephelometry to quantify IgM, all 26 patients (100%) showed at least a minor response, with 2 (8%) complete responses, 15 (58%) partial responses and 9 (35%) minor responses (49).

Most recently, the mTOR inhibitor everolimus (RAD-001) was studied in a 50-patient phase II trial of daily oral treatment with a dose of 10 mg (16, 50). The overall response rate was 70%, with a partial response of 42% and an estimated progression-free survival of 75% and 62%, respectively, at 6 and 12 months. 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 trial of the Akt inhibitor perifosine was conducted in 37 WM patients (51). In this study, the overall response rate was 35%, with 4 patients (11%) achieving a partial response. The median

Table III. *Novel therapeutic agents.*

Study (Ref.)	Regimen	N	Phase	ORR (%)
46	Bortezomib	27	II	78
39	Bortezomib	26	II	84
47	Bortezomib + Dexamethasone + Rituximab (upfront)	23	II	96
44	Thalidomide + Rituximab	23	II	78
45	Lenalidomide + Rituximab	16	II	67
50	Everolimus	50	II	70
51	Perifosine	37	II	35
48	Bortezomib weekly + rituximab (relapsed)	37	II	81
49	Bortezomib weekly + rituximab (upfront)	37	II	92
54	Bendamustine + rituximab (upfront)	42	II	96
52	Atacicept	4	I	NR

ORR = overall response rate; NR = not reported.

progression-free survival was 12.6 months. Perifosine was generally well tolerated; adverse events related to therapy were cytopenia (grade 3-4, 13%), gastrointestinal symptoms (grade 1-2, 81%) and arthritis flare (all grades, 11%) (15).

Atacicept, a soluble fusion protein between the IgG_1 Fc domain and the TACI (transmembrane activator and CAML interactor) receptor, binds to and neutralizes the B-cell survival factors B-lymphocyte stimulator and proliferation-inducing ligand APRIL. Atacicept was well tolerated in a phase I study in patients with multiple myeloma and WM, in which 16 patients with advanced disease (12 with multiple myeloma and 4 with WM) received 1 cycle of 5 once-weekly s.c. injections of atacicept. Patients with stable disease after cycle 1 entered an extension study. Of the 4 patients with WM, 3 were progression-free after cycle 1 (52).

Bendamustine hydrochloride was recently tested in combination with rituximab in 42 patients with untreated WM (16, 53, 54). Encouragingly, this treatment produced an overall response rate of 96% and lower incidences of grade 3 and 4 cytopenias, infectious complications and alopecia when compared with a standard treatment of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone.

FUTURE DIRECTIONS OF NOVEL THERAPEUTIC AGENTS

Ongoing and planned future clinical trials include those using protein kinase C (PKC) inhibitors such as enzastaurin, new proteasome inhibitors such as carfilzomib, histone deacetylase (HD) 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 samples (55). A phase II study of this agent is ongoing in patients with relapsed or refractory WM (40). Carfilzomib is a selective inhibitor of the chymotrypsin-like activity of the immunoproteasome and constitutive proteasome. Preclinical studies are under way to support the initiation of future phase II clinical trials in WM. Similarly, panobinostat and other HD inhibitors have been tested in the preclinical setting in WM and a phase II clinical trial of panobinostat has been initiated in patients with relapsed or refractory WM. Finally, the new humanized CD20-directed 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 WM therapy, especially the side effects observed with rituximab, the phase II ofatumumab trial may lead the way to change monoclonal therapeutic options in WM patients. In addition, multiple other novel therapeutic agents are currently being tested in the preclinical setting. As mentioned before, these include MDX-1097, PR-047, BEZ-235, midostaurin (PKC-412), AZD-0635 and dovitinib lactate (TKI-258) (41-43).

CONCLUSIONS

There has been a momentous shift in the understanding of WM and mechanistic ways to manipulate WM cell lines. New therapeutic agents have revolutionized the options for patients with WM. Future combinations of these agents should increase overall response rates and decrease toxicities. In the future, these compounds may provide WM patients with greater responses, longer remissions and a better quality of life than traditional chemotherapeutics.

DISCLOSURES

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