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Waldenstrom's Macroglobulinemia: Recent Advances in Biology and Therapy

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Abstract

Waldenstrom's macroglobulinemia (WM) is a B-cell disorder characterized by bone marrow infiltration with clonal lymphoplasmacytic cells (LPCs), along with an IgM monoclonal gammopathy. Recent studies have led to several insights into disease biology as well the development of an International Staging System. Patients with asymptomatic macroglobulinemia should be observed without therapy. Options for frontline therapy include alkylating agents, nucleoside analogs, and rituximab, either as monotherapy or in combination. Although objective responses are common, complete remissions are infrequent. Several novel agents including proteasome inhibitors, and thalidomide, as well as high-dose chemotherapy and stem cell transplantation are being incorporated into therapeutic armamentarium in WM and show promising activity. This report provides an update on recent advances in biology and treatment of this disease.

Introduction

Waldenstrom's macroglobulinemia (WM) is defined as a B-cell neoplasm characterized by a lymphoplasmacytic infiltrate in the bone marrow, with an associated immunoglobulin (Ig) M paraprotein. Since the first description by Dr. Jan Waldenstrom in 1944, WM has evolved conceptually from a clinical syndrome to a distinct clinicopathologic entity.[1] It has an overall incidence of approximately 3 per million persons per year, accounting for approximately 1–2% of hematologic cancers and approximately 1,500 new cases diagnosed per year in the United States.[2,3] In contrast to myeloma, WM primarily affects Caucasians and is rare in Blacks, who represent only 5% of cases. At present, the etiology of WM remains unknown. It is believed to be predominantly a sporadic disease; however, one study has suggested a high familial incidence, with about 18% of WM patients having at least a first degree relative with a B-cell neoplasm.[4] The main risk factor for the development of WM is pre-existing IgM-monoclonal gammopathy of undetermined significance (MGUS), which represents a preneoplastic condition and confers 46 times higher relative risk than in the general population.[5]

Biology and Genetics of WM

The cell of origin of the malignant clone is thought to be a post-germinal center B-cell before terminal differentiation to plasma cells.[6] A defining feature of the disease is that the tumor cells express monoclonal IgM. It has been suggested that tumor cells carry the normal machinery for class switch recombination (CSR), but are either unable to do so, or for unclear reasons do so very inefficiently in culture or in vivo.[6–8] Tumor cells express the enzyme activation induced deaminase (AID) thought to be critical for CSR, and the mechanism of the putative abnormalities in CSR are unclear. The presence of somatic

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hypermutation defines the dominant phenotype, although a minor unmutated phenotype has also been described. Mutated WM was shown to lack the expression of CD27, which may or may not represent a distinct memory B-cell precursor.

Deletion of the long arm of chromosome 6 (6q-) is the most frequent cytogenetic abnormality in WM[9]; however, it is not specific for WM and may be seen in other B-cell lymphomas. These deletions usually involve chromosome bands 6q21-q23, with the q23 region being the most commonly deleted. It has been suggested that patients with this deletion may have more aggressive disease and shorter survival; however, these data need further confirmation.[9] Of interest, the deletion in 6q may include a gene, PRDM1/Blimp1, a master regulator of plasma cell differentiation. WM cells lack Ig heavy chain translocations typically seen in myeloma. Although some rare cases have clones with IgH translocations,[10] these events are now believed to be secondary genetic events associated with disease progression. Deletions of 13q14 and 17p13.1 are uncommon at diagnosis, but may be observed in 15% of patients at the time of disease progression.[11]

Studies of gene expression profiling (GEP) in WM have suggested that the tumor cells may be closer to B-cell chronic lymphocytic leukemia (CLL) than to myeloma.[12] This may be in part due to the differentiation status of the tumor cells studied and the methodology used to isolate tumor cells for these studies. Intraclonal diversity at the level of cellular differentiation has made the GEP studies of bulk tumor cells in WM challenging. Nonetheless, GEP studies have identified several novel potential therapeutic targets in WM. For example, clonal cells of WM express high levels of interleukin 6 (IL-6), consistent with the clinical observation of high C-reactive protein levels in the serum of WM patients.[13] Gutierrez and colleagues confirmed the upregulation of IL-6 in WM.[14] More recently, both microRNA profiling,[15] as well as antibody based protein microarrays, have also been applied to study WM. Using protein profiling, investigators showed that proteins up-regulated by more than 2-fold in tumor cells included Ras family proteins, such as Rab-4 and p62DOK, and Rho family proteins, such as CDC42GAP and ROKalpha.[16] As with CLL, the disease may be subtyped based on the presence of somatic hypermutation. In WM, the presence of somatic hypermutation defines a predominant mutated subset and a minor unmutated subset indicative of naive B-cell origin. CD27 is a tumor necrosis factor receptor family glycoprotein that has been identified as a marker for normal memory B cells.[17] In mutated WM, the tumor cells may lack CD27, suggesting an unusual memory B-cell origin. Normal IgM+ D+ CD27− memory B cells with low levels of somatic hypermutation have recently been identified. Though the value of CD27 expression remains uncertain, somatic hypermutation undeniably defines memory B-cell origin in most WM.[17]

The malignant clone in WM spans the spectrum of lymphoplasmacytic differentiation. It has been argued that this may represent aberrant plasma cell differentiation, which is supported by aberrant expression of plasma cell differentiation factors such as XBP1, PAX5, and Blimp1 in these cells.[18] However, the underlying mechanism of such an aberrant differentiation, if any, remains to be defined. It is possible that the differentiation status of tumor cells is influenced by signals from the tumor microenvironment and genetic lesions in the tumor cells. Differentiation status may also impact outcome in WM. For example, patients with high tumor burden and a paradoxically low IgM may have adverse outcome.[18,19] An interesting feature of the disease is the finding of an increased number of mast cells in the bone marrow of patients with WM.[18] The role of mast cells in disease pathogenesis has not been fully elucidated. However, it appears that they may enhance the viability and proliferation of tumor cells and stimulate immunoglobulin production through the expressions of CD40L, vascular endothelial growth factor (VEGF), B-lymphocyte stimulator protein (B-LYS), and platelet-derived growth factor (PDGF)-alpha.[20] A role for CD27-CD70 interactions in the pathobiology of WM has also been implicated.[21] However,

in spite of considerable strides in understanding WM biology, major gaps remain. Development of in vitro and in vivo model systems and improved understanding of the genetics and biology of tumor cells and their microenvironment will facilitate the development of novel approaches for WM.

Diagnosis and Clinical Aspects

The diagnosis of WM is made on the basis of infiltration of the bone marrow by a lymphoplasmacytic clone and the presence of IgM monoclonal protein. The Second International Workshop on WM eliminated the requirement that a certain minimum threshold serum concentration of IgM must be present for the diagnosis. Entities typically considered in differential diagnosis include splenic marginal zone lymphoma, MGUS, myeloma, CLL, or mantle cell lymphoma.[22]

Patients may have symptoms attributable to tumor infiltration, circulating IgM, tissue deposition of IgM, or autoantibody activity of IgM. Symptoms of cytopenias, specifically anemia related to replacement of the bone marrow with tumor cells, are most common. Fatigue is a common presentation of WM. 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. Approximately one-fourth of patients are asymptomatic and diagnosed incidentally. Peripheral blood smear typically shows striking rouleaux formation and lymphocytosis and monocytosis may be observed in some patients. Leukopenia and thrombocytopenia (due to marrow infiltration) may also be present, but the platelet count is rarely less than 50,000/μL. A clinically important bleeding diathesis may occur due to hyperviscosity and an interference with clotting factor and platelet function.

The most consistent feature of the bone marrow or lymph nodes of patients with WM is the presence of pleomorphic B-lineage cells at different stages of maturation, such as small lymphocytes, lymphoplasmacytoid cells, and plasma cells. Bone marrow is infiltrated in a predominantly intertrabecular pattern. A significant increase in the number of mast cells has been noted in bone marrow biopsies of WM patients, as well as the presence of Dutcher bodies—cytoplasmic inclusions that are either invaginated into or are overlying the nucleus and are positive on a periodic acid-Schiff reaction.[23] The cells express pan B-cell markers including CD19, CD20, and CD22, but lack CD10, CD38, FMC7, and cytoplasmic Ig. CD5 and CD23 are expressed in 5–20% and 35% of the cases, respectively.

The pathologic hallmark of WM is bone marrow involvement with IgM secreting lymphoplasmacytic lymphoma (LPL). LPL is defined as a lymphoma composed of small lymphocytes that show maturation to plasma cells without any of the clinical, morphologic, or immunophenotypic features of other lymphoproliferative disorders.[24] However, this entity was one of the least reproducible in the Non-Hodgkin's Lymphoma Classification Project. Of note, LPL may be nonsecretory or be associated with non-IgM (IgG or IgA) monoclonal proteins. The diagnosis cannot be made in the absence of infiltration of bone marrow by clonal lymphoplasmacytic cells.[24] A bone marrow biopsy allows an accurate evaluation of both the extent and pattern of bone marrow infiltration and is therefore essential for the assessment of patients suspected of having WM.

Several studies have evaluated the effects of clinical and laboratory variables on patient outcome. Recently, an International Prognostic Scoring System (IPSS-WM) was developed to optimize risk adapted therapy and facilitate clinical research in WM. Five adverse covariates were identified: advanced age (>65 years), hemoglobin less than or equal to 11.5 g/dL, platelet count less than or equal to 100 x 10^9/L, β2-microglobulin greater than 3 mg/L,

and serum monoclonal protein concentration greater than 7.0 g/dL. Low-risk patients with none or one of the adverse characteristics and advanced age; intermediate-risk patients with 2 adverse characteristics or only advanced age; and high-risk patients with more than 2 adverse characteristics had 5-year survival rates of 87%, 68%, and 36%, respectively.[25] A recent update of the U.S. Intergroup trial identified serum LDH as an additional prognostic variable, which added to the prognostic information provided by IPSS-WM.[26] An important insight from the scoring system is the recognition that age is the most dominant prognostic variable. These prognostic models may need to be revisited in the context of newer therapies, longer follow-up with current therapies in WM may be necessary.

Additional Clinical Considerations in WM

Clinical symptoms in WM are related either to the monoclonal IgM or the tissue infiltration by the clone. Symptoms related to hyperviscosity can be observed in up to 20–30% of patients, and may include neurologic complaints such as blurring or loss of vision, headache, vertigo, nystagmus, dizziness, tinnitus, sudden deafness, diplopia, or ataxia. Marked hyperviscosity can rarely lead to confusion, dementia, disturbances of consciousness, stroke, or coma. When accompanied by anemia, hyperviscosity and the associated plasma volume expansion may precipitate or aggravate congestive heart failure. Although the correlation between serum viscosity and clinical manifestations is not precise, symptoms often begin when serum viscosity is greater than 4 CP, and most patients are symptomatic when serum viscosity is greater than 6 CP. The decision to initiate treatment with plasmapheresis should be on the basis of the patient's symptoms and physical findings, rather than on the magnitude of the viscosity measurement. Transient increases in IgM titers (also called IgM flare) have been reported in 54% of patients after initiation of single-agent rituximab (Rituxan, Genentech) therapy. These levels may persist for up to 4 months and do not indicate treatment failure, but they may necessitate plasmapheresis to reduce hyperviscosity.

Neurologic abnormalities may manifest with distal, symmetric, and slowly progressive sensorimotor peripheral neuropathy causing paresthesias and weakness. Funduscopic abnormalities are sometimes noted, namely the presence of dilated, segmented, and tortuous retinal veins, giving a "sausage link" appearance associated with hyperviscosity. Patients may also develop symptoms due to cryoglobulinemia including Raynaud phenomenon, urticaria, purpura, acral cyanosis, and/or tissue necrosis. Infiltration in the central nervous system, referred to as Bing-Neel syndrome, is rare. Cerebrospinal fluid analysis may show lymphocytic pleocytosis, elevated protein, and IgM kappa or lambda light chain restriction; cytology results are variable and imaging is frequently abnormal.

Therapy

Principles of Therapy

Patients should receive therapy only if they have symptoms or signs related to WM or specific laboratory abnormalities, and not based solely on the serum monoclonal protein level. In a recent update of the U.S. Intergroup trial, only 21% of patients with asymptomatic WM eventually required therapy with a median follow up of 8 years.[26] Patients with a disease-related hemoglobin level less than 100 g/L, platelet count less than 100 x 10^9/L, bulky adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold-agglutinin disease, or evidence of disease transformation should be considered for therapy.[27] Therapeutic options include nucleoside analogs, alkylating agents, and rituximab either alone or in combination (Tables 1 and 2). Due to paucity of randomized clinical trials in WM, it is impossible to recommend the use of one first-line agent or regimen over another. A recent international consensus panel suggested individualizing therapy based on the presence of cytopenias, need for rapid

disease control, age, and candidacy for stem cell transplant.[28] With combination therapy, objective response rates (ORR; including minor responses) may exceed 80%, but complete response (CR) rates are 0–15%, and data on long-term outcome and durability of these responses are lacking. For patients eligible for autologous transplant, prolonged exposure to alkylating agents and nucleoside analogs should be limited in view of the potential effect on stem cell collection. For the treatment of relapsed disease, the use of alternate first-line agents, reuse of a first-line agent, use of combination myelotoxic chemotherapy, and use of thalidomide as a single agent or in combination therapy has been recommended.[28] An overview of selected therapeutic trials in WM is provided in Table 2.

Rituximab-based Combinations

Due to its activity, tolerance, and synergy with other agents, rituximab is now a component of most frontline and salvage regimens in WM. Response rates to single-agent rituximab range from 30–50%, and may depend in part on the nature of polymorphisms of activating Fc gamma receptors. As noted earlier, transient flares in IgM levels have been reported in nearly half of the patients treated with rituximab monotherapy.[29] Serum levels of soluble CD27 may be useful markers of disease activity in the setting of tumor flare.[30] Nonetheless, the possibility of IgM flare has led to avoidance of single-agent rituximab in patients with high baseline levels of M protein. The synergy between rituximab and several agents has led to attempts to combine this antibody with several therapies. Below, we discuss some of the updated data on combination therapies in WM.

Combinations With Purine Analogs

Purine nucleoside analogs (PNAs) have been extensively studied in WM, both as single agents[19, 31] and as combination therapies. Response rates with single-agent PNAs range from 30–70%. Higher response rates have been observed in combination therapies. For example, Weber and coworkers observed an ORR of 94% (17% CRs) in 27 patients treated with a cladribine-based combination.[32] Tedeschi and associates administered rituximab, fludarabine, and cyclophosphamide (RFC) every 4 weeks for 6 courses to 19 patients with WM that resulted in 79% PR.[33] The RFC regimen, with oral fludarabine and cyclophosphamide, was used in 25 mostly pretreated patients with a PR rate of 69% and an MR rate of 9%.[34] Delayed responses (beyond 4–10 months) have been observed in some series. These trials confirm the significant activity of combinations that include rituximab and nucleoside analogs. Due to the kinetics of response, such regimens may be particularly useful when rapid disease control is required. However, these regimens also carry a significant risk of toxicity due to cytopenia and immune suppression, particularly in elderly patients. Another concern relates to recent reports suggesting increased incidence of Richter's transformation and development of myelodysplastic syndrome/leukemia in WM patients treated with nucleoside analog–containing therapy.[35,36] Nonetheless, it is important to remember that these agents can lead to durable responses in WM, and do have a track record for inducing long-term survival. In fact, nearly 20% of patients were alive at 10 years after single-agent fludarabine in the U.S. Intergroup trial.[26] It is also notable that in a small randomized trial, fludarabine was superior to a combination of cyclophosphamide, doxorubicin, and prednisone both in terms of response rates and durability of responses.[37]

Combination With Alkylating Agents

Rituximab has also been combined with alkylating agents such as chlorambucil or cyclophosphamide, which also have a long track record as active agents in WM. Dimopoulos and co-authors treated 72 WM patients with a frontline regimen consisting of dexamethasone, rituximab, and cyclophosphamide.[38] An objective response was documented in 83% of patients, including 7% CR, 67% PR, and 9% MR. Rituximab has also been combined with other regimens commonly used to treat lymphoma. Abonour and

colleagues[39] reported the outcome of 16 previously untreated patients treated with the combination of rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone (R-CHOP). This trial achieved a PR in 91% of patients, with a rapid median time to response. Ioakimidis and associates compared outcomes of patients treated with R-CHOP, rituximab plus cyclophosphamide, vincristine, and prednisone, or rituximab plus cyclophosphamide and prednisone, and observed that the ORR was quite similar.[40] Another agent with activity in lymphoplasmacytic lymphoma is bendamustine (Treanda, Cephalon), which has also been combined with rituximab.[41] Combinations of rituximab with alkylating agents are useful options for patients who are potential candidates for stem cell transplantation. Less aggressive regimens are also attractive options for older patients with comorbidities who are unlikely to tolerate more aggressive regimens.

Combination With Bortezomib or Immunomodulatory Drugs

Bortezomib and immunomodulatory drugs (thalidomide and lenalidomide) have changed the therapeutic landscape in myeloma. Bortezomib has been evaluated in 2 prospective phase II studies. Treon and coworkers treated 27 patients with up to 8 cycles of bortezomib. The ORR was 85%.[42] In the study conducted by the National Cancer Institute-Canada, the ORR with bortezomib monotherapy was 78%, with major responses observed in 44% of patients.[43] A recent multicenter study combined bortezomib with dexamethasone and rituximab for the primary therapy of patients with WM. Among the 23 treated patients, the ORR was 96% with 13% CRs.[44] However, a major concern with bortezomib in WM is the occurrence of peripheral neuropathy, requiring discontinuation of bortezomib in 61% of patients. Similar findings were noted in another study by Agathocleous and associates.[45] Use of alternate regimens (such as weekly dosing) may reduce neuropathy, but needs to be systematically tested. One potential advantage of bortezomib-based combinations may be the rapid reduction of IgM levels, although it is not known at present which patients are best suited for this approach. An interesting observation with bortezomib is the potential discordance between serum IgM levels and bone marrow responses, suggesting that for some patients, bortezomib may be inhibiting IgM secretion independent of direct tumor cell killing; the reason for this phenomenon remains to be elucidated.[46] Thus, clinicians need to be aware of the possible disagreement of serum IgM levels and clinical response to bortezomib, and a bone marrow biopsy should be considered to clarify response. Together, these data support consideration of bortezomib and bortezomib-based combinations for patients who failed treatment with alkylating agents, nucleoside analogs, and rituximab.

Preclinical studies have suggested a possible synergistic effect of rituximab with thalidomide and lenalidomide, particularly at the level of antibody dependent cytotoxicity. A combination of thalidomide plus rituximab in 25 patients resulted in overall and major response rates of 72% and 64%, respectively.[47] This regimen therefore has activity and may be a consideration, in particular for patients who present with cytopenias. A combination of lenalidomide and rituximab in WM was also found to be active, but an acute decrease in hematocrit in 13 of 16 patients attributable to lenalidomide was observed and led to cessation of further enrollment in this study.[48] Lenalidomide-related anemia was observed even at doses as low as 5 mg day and occurred in the absence of hemolysis or other cytopenias. The mechanism for pronounced anemia in WM patients receiving lenalidomide remains to be determined, and the use of this agent in WM patients remains investigational.

Stem Cell Transplantation

The concept of dose response correlation has led to consideration of high-dose chemotherapy and stem cell transplantation in WM. Most published studies have evaluated patients with extensive prior therapy, and demonstrated the feasibility of durable responses with this approach.[49] For example, in the analysis of European Bone Marrow Transplant

registry, the 5-year progression-free and overall survival rates were 33% and 61%, respectively.[49] High-dose chemotherapy with autologous peripheral blood stem cell transplantation may therefore be an option, specifically in patients with high-risk disease. Allogeneic or nonmyeloablative allogeneic transplantation has also been attempted in small studies, but carries higher (25–35%) transplant-related mortality. The role of high-dose chemotherapy and stem cell transplantation in WM requires evaluation in the context of prospective trials, preferably focusing on patients with high-risk disease, and as a part of frontline therapy.

Novel Therapies

Alemtuzumab

Alemtuzumab (Campath, Genzyme) is a humanized monoclonal antibody that targets CD52, an antigen widely expressed in tumor cells as well as in mast cells increased in the bone marrow of WM patients. In a phase II trial, the ORR with alemtuzumab therapy was 76%, including 32% PRs.[50] However, treatment-related toxicity observed in early studies may limit the utility of this agent in WM.

Radioimmunotherapy

Radioimmunotherapy directed to CD20, 90Y-Ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals) or iodine^{131} tositumomab (Bexxar, GlaxoSmithKline) in WM has been limited since the high level of bone marrow involvement commonly seen in WM precludes their use. However, case reports have shown that these therapies may be effective in WM patients with less than 25% bone marrow involvement. Epratuzumab (UCB) is a new radio-conjugated humanized anti-CD22 antibody currently in development in non-Hodgkin high grade and indolent lymphomas. Further experiences are required before testing this new agent in WM.

Signaling Pathway Inhibitors

Signaling via the PI3K pathway, including Akt, mammalian target of rapamycin (mTOR), and protein kinase C (PKC) has been involved in survival and proliferation of several cancer types in addition to WM. Perifosine (Keryx Biopharmaceuticals) is a novel Akt inhibitor that belongs to a class of lipid-related compounds called alkyl-phospholipids. [51] A phase II trial of single-agent perifosine in 36 patients with relapsed or relapsed/refractory WM reported an ORR of 35%, with 2 (5%) major responses and 11 (30%) minor responses.[51] Perifosine was generally well tolerated. Phase II trials of single-agent mTOR inhibitor everolimus (Afinitor, Novartis) and PKC inhibitor enzastaurin (Eli Lilly) in patients with relapsed or refractory WM have also been carried out.

Other Investigational Agents

Over the past several years, there has been a flurry of early-stage small clinical trials testing several agents in patients with WM. In many settings, the rationale for testing agents in WM. A phase II trial of single-agent imatinib (Gleevec, Novartis) in patients with relapsed or refractory WM reported that at 3 months of therapy, 46% of patients achieved minor response.[52] However, imatinib led to toxicity requiring cessation of therapy in 23% of patients. Bcl-2 regulates apoptosis and resistance to chemotherapeutic agents. In vitro studies have shown that Bcl-2 is expressed in WM cells and that downregulation of Bcl-2 and increased cytotoxicity may be achieved with Bcl-2 inhibitors. A phase I/II clinical trial of Bcl-2 inhibitor G3139 (oblimersen sodium, Genta) conducted in patients with relapsed or relapsed/refractory WM showed favorable tolerability but minimal activity.[53] The SGN-70 humanized monoclonal antibody bound 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. TACI-Ig, atacicept (ZymoGenetics) is a compound that contains a soluble receptor fusion protein composed of the extracellular domain of TACI. The Fc portion of a human IgG binds to both APRIL (A Proliferation-Inducing Ligand) and B-LYS, members of the tumor necrosis factor family that promotes B-cell survival. An open-label, dose-escalation phase I study of atacicept enrolled 16 patients with active progressive WM in 2006.[54] No objective responses were observed in this study. Additionally, preclinical evidence suggests that the CXCR4 inhibitor AMD3100, resveratrol, triterpenoids CDDO and CDDO-Im, 2-cyano-3, 12-dioxoolean-1,9-dien-28-oic acid (CDDO), its methyl ester derivative (CDDO-Me), imidazolide derivative (CDDO-Im), as well as HMG-CoA reductase inhibitor simvastatin, may have potential activity in WM.

Conclusions

There have been significant advances in the knowledge of the pathogenesis and the development of novel therapeutic options in WM. However, major gaps still remain, particularly at the level of understanding the etiology and the molecular basis of the marked variation in clinical outcome. It is therefore essential that future investigations continue to dissect the biology of WM and understand the tumor and host-related factors linked to disease progression. At a therapeutic level, though current therapies yield high ORR, CR rates are still very low. For most of the novel therapies, durability of responses and the ultimate impact on long-term survival remains to be determined. Improved understanding of WM biology may allow optimal and risk-adapted use of current and novel therapies towards improved survival.

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Table 1

Suggested Treatment Options for Waldenstrom Mcroglobulinemia

Asymptomatic patients
• Observation alone
First-line therapy
Patients requiring rapid disease control
• Rituximab based combinations*
– Alkylating agents (eg, DRC, R-CHOP)
– Purine analogs (eg, FR)
– Bortezomib-based combinations (eg, BDR)
Patients not requiring rapid disease control
• Single agent therapy
– (eg, rituximab, chlorambucil, fludarabine)
• Combination therapy
– Alkylating agent-based (eg, RCD, CVP-R, CP-R)†
– Nucleoside analog-based (eg, FR)*
Salvage therapy
• Reuse of first-line agent (for patients relapsing ≥2 years following initial treatment)
• Alternate first-line agents (for patients relapsing <2 years after initial therapy)
• Combination therapy as above
• Bortezomib-based therapy
• Immunomodulatory drugs
• Alemtuzumab
• Bendamustine
• Stem cell transplantation

BDR=bortezomib, dexamethasone, rituximab; CPR= cyclophosphamide, prednisone, rituximab; CVP-R= cyclophosphamide, vincristine, prednisone; DRC= dexamethasone, rituximab, cytoxan; FR=fludarabine, rituximab; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

*Transient flares in IgM levels have been reported in nearly half the patients treated with rituximab monotherapy.

†For patients potentially eligible for autologous transplant, prolonged exposure to alkylating agents and nucleoside analogs should be limited prior to stem cell collection.

Table 2

Selected Therapeutic Trials in Waldenstrom Macroglobulinemia

Author	Regimen	Number of patients	ORR (%)	CR (%)	OS (mo)	PFS	Comments
Gertz et al[55]	Rituximab	69	52	0	NA	NA	Well-tolerated, possibility of IgM flare
Dimopoulos et al[56]	Cladribine	26	85	(3/26)	NA	NA	High risk of viral infections
Dhodapkar et al[19]	Fludarabine	182	36	2	88	49	OS at 5 years 58%
Dimopoulos et al[31]	Fludarabine	28	36	0	NA	NA	
Tamburini et al[57]	Fludarabine Cyclophosphamide	49	78	0	NA	NA	
Weber et al[32]	Cladribine, Cyclophosphamide Rituximab	27	94	17	73		Grade 3/4 neutropenia in 71%, serious infections in 35%
Tedeschi et al[33]	Fludarabine Cyclophosphamide Rituximab	19	79	5	NA	NA	Neutropenia observed in 82%
Vargaftig et al[34]	Fludarabine Cyclophosphamide Rituximab	25	78	0	NA	NA	Significant risk of infections
Leblond et al[37]	CAP	45	11	0	45	NA	
Abonour et al[39]	CHOP-R	16	100	0	NA	NA	Rapid median time to response
Ioakimidis et al[40]	CHOP-R CVP-R CP-R	23 16 19	96 88 95	17 12 0	NA	NA	P values not different. Higher incidence for neutropenic fever and treatment-related neuropathy for CHOP-R and CVP-R versus CP-R.
Dimopoulos et al[38]	DRC	72	83	7	NA	2 year PFS, 67%	Well-tolerated; grade 3/4 neutropenia in 9%.
Treon et al[42]	Bortezomib	27	85	0	NA	NA	
Treon et al[44,58]	Bortezomib Dexamethasone Rituximab	23	96	13	NA	NA	Most common toxicity: peripheral neuropathy (61%). Rapid reduction in IgM
Treon et al[47]	Rituximab Thalidomide	25	72	0	NA	NA	May be considered in patients presenting with cytopenias

CAP=cyclophosphamide, doxorubicin, prednisone; CHOP-R=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; CP-R=cyclophosphamide, prednisone, rituximab; CR=complete response; CVP-R= cyclophosphamide, vincristine, prednisone; DRC=dexamethasone, rituximab, cyclophosphamide; NA=not applicable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.