Are New Treatment Options Shifting How and When We Treat Waldenström Macroglobulinemia?

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Abstract

The introduction of new agents for the treatment of Waldenström macroglobulinemia has had a dramatic impact on survivorship in this disease. Earlier diagnosis has led to a reduced frequency of hyperviscosity. The MYD88 mutation appears to define 90% of patients with Waldenström macroglobulinemia and helps differentiate it from other disorders. Bendamustine and rituximab is a highly active regimen for the treatment of this disease as is cyclophosphamide, dexamethasone, and rituximab. Other agents that show high activity include purine nucleoside analogues, bortezomib, carfilzomib, everolimus, and ibrutinib.

Key words: Waldenström macroglobulinemia; hyperviscosity; bendamustine; ibrutinib; proteasome inhibitors; purine nucleoside analogs

Introduction

Waldenström macroglobulinemia is defined by the World Health Organization and the International Waldenström's Working Group as the presence of bone marrow lymphoplasmacytic lymphoma associated with a monoclonal IgM protein of any size. The bone marrow morphology shows both CD38 expressing plasma cells and CD20 expressing lymphoplasmacytic cells. A monoclonal protein is invariably visible on the serum protein electrophoresis. Immunofixation identifies an IgM heavy chain. One of the defining syndromes of Waldenström macroglobulinemia is the development of hyperviscosity due to the impact of pentameric IgM on the flow of serum. The most common signs of hyperviscosity are oronasal bleeding or blurred vision secondary to retinal hemorrhage.

IgM monoclonal serum proteins represent 18% of all monoclonal proteins seen. Since monoclonal gammopathy of undetermined significance (MGUS) is seen in 3% of adults over the age of 70, 1 adult in 200 will have an IgM monoclonal protein. However, only 1.9% of non-Hodgkin lymphoma are Waldenström macroglobulinemia, with a median age at diagnosis of 73 and an overall annual age-adjusted incidence of 3.8 per million. A family history is obtained in 4.3%.[1] Waldenström macroglobulinemia is twice as common in men as in women (5.4 vs. 2.7 per million per year) and is more common in whites (4.1 per million per year) than in blacks (1.8 per million per year). A significant annual percentage increase is being seen in patients over the age of 70.[2] Age has a profound impact on outcome with median survival of approximately four years for patients age 80 or over compared with an 85% survival at four years for patients under the age of 60.[3] The MYD88 mutation does not define Waldenström macroglobulinemia, but is observed in 85% to 100% of patients. MYD88 mutations were significantly associated with the presence of 6q deletions. MYD88 is also seen in IgM MGUS, but only rarely seen in diffuse large-cell lymphomas or marginal zone lymphomas and is not seen in multiple myeloma or CLL.[4] Approximately 50 % of patients have some aberrancy on conventional cytogenetics and/or fluorescence in situ hybridization (FISH) analysis, with the most common abnormalities being the deletion (del) of the long arm of chromosome 6 (22% to 46%), del13q14 (13% to 15%), trisomy 18 (11% to 23%), trisomy 4 (4% to 12%), and delp53 (4% to 23%). Trisomy 4 is a unique feature and is occasionally the only abnormality observed in WM.

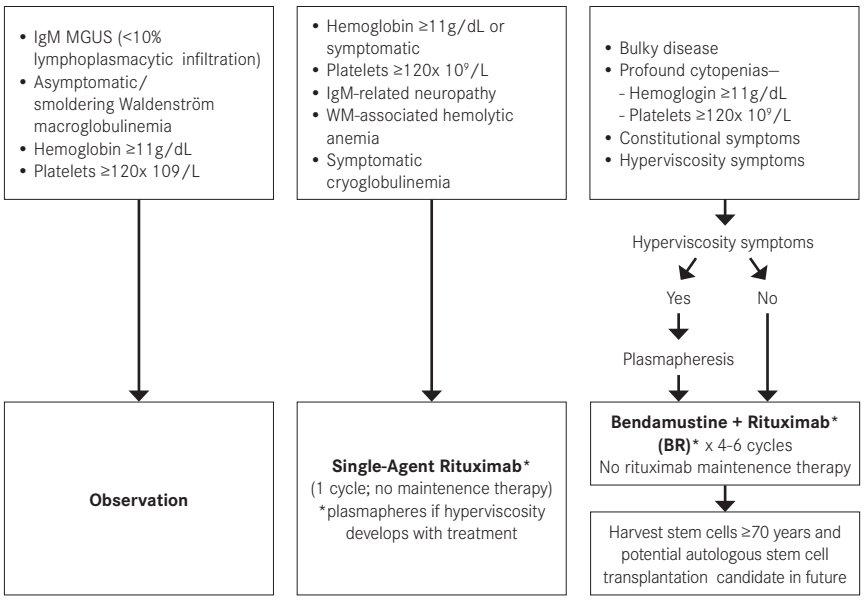
Goals of Therapy

The most common question faced by clinicians is determining when is the appropriate time to abandon a regimen for lack of efficacy and change to a second regimen? The answer to this question is driven by the endpoints that led to the initiation of therapy. Waldenström macroglobulinemia does not always need therapy. Patients may be diagnosed with the disorder, but lack sufficient symptoms related to anemia, lymphadenopathy, or constitutional symptoms to warrant intervention. Patients with so-called smoldering Waldenström macroglobulinemia can be monitored without therapeutic intervention, although the rate of progression into overt disease is substantial, and most patients ultimately require therapy. Fludarabine is highly active in the treatment of Waldenström macroglobulinemia and has been shown, in a phase III trial, to be superior to chlorambucil in terms of progression-free and overall survival. Moreover, the risk of secondary malignancy with fludarabine

is <5%, and transformation into large-cell lymphoma is approximately 10% at eight years.[5]

The use of dexamethasone-rituximab-cyclophosphamide has also been investigated in Waldenström macroglobulinemia in large cohorts. Age has a profound impact on outcome. Patients under the age of 65 have an 80% survival at 100 months compared with <40% in patients over the age of 65. Nearly half of patients with Waldenström macroglobulinemia die of unrelated causes, reflecting the indolent nature of this lymphoma. With the dexamethasone-rituximab-cyclophosphamide regimen, depth of response did not translate into improved survival, and patients achieving a very good partial response (VGPR) or better had the same survival as patients achieving a minor response.[6] Given the activity of both cyclophosphamide and fludarabine, combining them into fludarabine-cyclophosphamide-rituximab (FCR) shows a very high activity level. The response rate is 80%, VGPR of 32.5%, and an event-free survival of 77 months, independent of stage or prior therapy. Among 40 patients reported, 2 developed MDS and 1 large-cell transformation was seen. The regimen, other than being highly myelosuppressive, is well tolerated.[7] Both cladribine and pentostatin show significant activity in the treatment of Waldenström macroglobulinemia and are alternative purine nucleoside analogs that could be considered.[8,9] Single-agent rituximab use is to be discouraged in favor of higher-response-rate combinations.

FIGURE 1. Mayo Clinic M-SMART Guidelines for the Treatment of Waldenström Macroglobulinemia. With permission *Mayo Clinic Proceedings*.



Proteasome inhibitors, both bortezomib and carfilzomib, have been used in the treatment of Waldenström macroglobulinemia. Bortezomib combined with rituximab and dexamethasone resulted in a response rate of 85%. Rituximab was administered in this regimen in cycles 2 and 5 in an effort to reduce the risk of flare, which was seen in only 11%. This regimen, however, given in a 1, 4, 8, 11 schedule, resulted in peripheral neuropathy in 46% of patients. In a large study involving a large cohort of patients treated with bendamustine-dexamethasone-rituximab, median IgM level reported between cycle 1 and cycle 5 fell from 4000 to approximately 1700, and complete responses were seen in two patients; but time to maximum response after addition of BDR took as long as one year. With this regimen, overall survival exceeded five years.[10] Bortezomib has also been combined with rituximab and cyclophosphamide and demonstrated responses in 14 of 15 patients, including one complete response.[11]

The use of carfilzomib has also been investigated in Waldenströmm macroglobulinemia. Carfilzomib administered on days 1, 2, 8, 9 of each cycle with rituximab, and dexamethasone on days 2 and 9 of each cycle were administered to 31 patients. The overall response rate was 87% with 36% ≥VGPR. Median time to response was 2.1 months, and no neuropathy >grade 1 was seen.[12]

Everolimus shows activity in the treatment of chemotherapy refractory Waldenström macroglobulinemia. Sixty patients with advanced disease achieved an overall response rate of 50% and a clinical benefit rate of 73%. Median time to response was two months. Median progression-free survival was 21 months. Unfortunately, grade 3 or higher toxicities were observed in 67% of patients.[13]

Autologous stem cell transplantation is active in patients with Waldenström Macroglobulinemia. A review of registry data from Europe covering 158 patients demonstrated partial response (PR) or better in 134 patients, with a median event-free survival of over four years and a median overall survival not reached at eight years.[14] The East German Lymphoma Study Group reported a phase III trial of R-CHOP versus R-bendamustine. Forty-one patients in this cohort had Waldenström macroglobulinemia. Researchers reported that 22 received bendamustine and 19 received R-CHOP. The median progres-

sion-free survival for R-CHOP-treated patients was 36 months versus not reached for R-bendamustine. At analysis, 4 relapses (18%) in the bendamustine group and 11 relapses (58%) in the R-CHOP group were reported. The median progression-free survival was 69.5 months for the bendamustine group and 28.1 months for the R-CHOP group (P = .003).

Ibrutinib, the first-in-class Bruton tyrosine kinase inhibitor, was administered at a dose of 420 mg for two years to patients with one prior therapy. Median time to response was four weeks. The median IgM fell from 3610 to 1340, and the median hemoglobin rose from 10.5 to 12.6. Overall response rate was 61.9%, VGPR 11.1%, and the median duration of response has not been reached. Neutropenia was seen in 19%, thrombocytopenia in 14%; other significant side effects included diarrhea, bleeding, and atrial fibrillation.[15] The rate of response to ibrutinib in patietns with Waldenström macroglobulinemia was dependent on MYD88 status, with 95% of patients with mutated MYD88 responding to therapy and only 60% of wild type MYD88 responding to therapy. When both MYD88 and CXCR4 were unmutated, the response rate fell to 60% in patients with MYD88.[15] When patients were wild type for CXCR4 and MYD88, there were no ibrutinib responses. A second trial of 31 patients who were rituximab refractory reported a response rate of 84%, with a PR of ≥65%. Adverse events occurred in 94% and two patients with wild type MYD88 progressed on therapy.[16] The agent is approved for any line of therapy in North America, Europe, and Japan. A recent report indicated a risk of atrial fibrillation of 10.7%.[17]

Summary

Patients with IgM MGUS or asymptomatic Waldenström macroglobulinemia without cytopenias may be safely observed. Patients with bulky disease, constitutional symptoms, hyperviscosity, or evidence of bone marrow failure can be treated with bendamustine-rituximab, proteosome inhibitor/rituximab,dexamethasone-rituximab-cyclophosphamide, rituximab-ibrutinib is currently being tested (NCT 02165397). Stem cell transplantation remains an option for younger patients with Waldenström macroglobulinemia (Figure). For relapsed patients, repeating the original therapy if responses are longer than three years, is reasonable. Alternative therapies include purine nucleoside analogues, bortezomib, everolimus, carfilzomib, and ibrutinib. Active clinical trials are investigating various combinations, including rituximab-bendamustine-ibrutinib, rituximab-ibrutinib, and lenalidomide-ibrutinib, which will further improve the outcomes for these patients.

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