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Prognostic Factors and Indications for Treatment of Waldenström's Macroglobulinemia

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Abstract

Waldenström's Macroglobulinemia (WM) is characterized by the presence of an IgM monoclonal protein regardless of its size, 10% or more bone marrow infiltration by small lymphocytes with a plasmacytoid or plasma cell differentiation. These cells usually have the following markers: IgM+, CD5⁻, CD10⁻, CD19⁺, CD20⁺ and CD23⁻. Chronic lymphocytic leukemia as well as other lymphoproliferative disorders such as mantle cell, marginal zone and mucosa-associated lymphoid tissue (MALT) lymphoma must be excluded. Weakness or fatigue from anemia, fever, night sweats, or weight loss represent the most common symptoms. Hepatosplenomegaly may be a major feature. Anemia, thrombocytopenia, hyperviscosity or peripheral neuropathy may be prominent features. Systemic amyloidosis, renal insufficiency and cryoglobulinemia may also be seen. WM must be differentiated from smoldering Waldenström's Macroglobulinemia (SWM) which is an intermediate disease state characterized by an IgM protein ≥ 3 g/dL and/or a bone marrow containing $\geq 10\%$ bone marrow lymphoplasmacytic infiltration but no end-organ damage such as symptomatic anemia, constitutional symptoms, hyperviscosity, symptomatic hepatosplenomegaly or lymphadenopathy.

Keywords

IgM monoclonal gammopathy; Lymphoplasmacytic lymphoma; Lymphoproliferative disorder; Indolent lymphoma

Waldenström's Macroglobulinemia (WM) was described more than 70 years ago when Jan Waldenström reported two patients with a large homogeneous gamma globulin component that had a sedimentation coefficient of 19s to 20s and a molecular weight approaching 1 million Daltons.(1) Subsequently, this homogeneous gamma globulin was identified as an immunoglobulin and designated as IgM.

Waldenström's Macroglobulinemia is a distinct clinical entity characterized by an IgM monoclonal protein regardless of its size, $\geq 10\%$ bone marrow infiltration by small

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lymphocytes that show plasmacytoid or plasma cell differentiation. The typical immunophenotype shows surface IgM⁺, CD5⁺, CD10⁺, CD19⁺, CD20⁺ and CD23⁺. Approximately 90% of patients with Waldenström's macroglobulinemia harbor MYD88 L265P mutations.(2) Other lymphoproliferative disorders such as chronic lymphocytic leukemia and other lymphoma must be excluded.(3, 4) The clinical features include weakness or fatigue from anemia, fever, night sweats or weight loss, progressive symptomatic lymphadenopathy or splenomegaly, hemoglobin ≥ 10 g/dL or platelets $< 100 \times 10^9/L$ or hyperviscosity, severe sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency related to WM or symptomatic cryoglobulinemia.(5)

All patients with WM have a preceding IgM monoclonal gammopathy of undetermined significance (IgM MGUS) that is < 3 g/dL. Smoldering Waldenström's Macroglobulinemia (SWM) is an intermediate state in which the IgM monoclonal protein is ≥ 3 g/dL and/or a bone marrow contains $\geq 10\%$ bone marrow lymphoplasmacytic infiltration but there is no evidence of end-organ damage such as symptomatic anemia, constitutional symptoms, hyperviscosity, symptomatic lymphadenopathy or hepatosplenomegaly due to the plasma cell proliferative process. These patients progress to symptomatic WM, amyloidosis or lymphoma at a rate of 6% in the first year, 39% at 3 years, 59% at 5 years and 68% at 10 years. The percentage of lymphoplasmacytic cells in the bone marrow, size of the serum M-spike and the hemoglobin value are major risk factors for progression. At present, these patients should not be treated until they develop symptomatic WM.(6) . This approach is supported by the observation in SWM patients, who were followed until progression to active disease that the response rates and survival after institution of treatment for overt disease were similar to their counterparts who were treated promptly for symptomatic disease from outset.(7)

IgM Monoclonal Gammopathy of Undetermined Significance (IgM MGUS)

IgM Monoclonal Gammopathy of Undetermined Significance (IgM MGUS) consists of the presence of a monoclonal IgM protein in the serum < 3 g/dL and fewer than 10% lymphoplasmacytic cells in the bone marrow without clinical findings or symptoms. Two-hundred thirteen Mayo Clinic patients with IgM MGUS were recognized in the 11 counties of southeastern Minnesota from 1960-1998.(6) At diagnosis the median age was 74 years (range 24-94 years) with two-thirds older than 70 years and only 1% < 40 years of age. Fifty-eight percent were male while 42% were female. The M-protein ranged in size from unmeasurable (not quantifiable by densitometry) to 2.6 g/dL with a median of 1.2 g/dL. The IgM value on nephelometry was < 300 mg/dL in 15%. Seventy percent were IgM kappa while IgM lambda was found in the remaining 30%. The uninvolved immunoglobulins (IgG and/or IgA) were reduced in 35%. The monoclonal light chain value was < 100 mg/24 hours in all but three patients. When present, anemia, thrombocytopenia or renal insufficiency was unrelated to the lymphoplasmacytic proliferation.

Seventy-one percent died during the 1,567 person-years of monitoring. Non-Hodgkin lymphoma developed in 17 persons, WM in 6, while 3 developed AL amyloidosis and 3 others had chronic lymphocytic leukemia. The expected rate of progression in the Iowa SEER registry was increased 1.8-fold while disease progression was increased 15.9-fold

(Table 1). The cumulative probability of progression to one of these disorders was 10% at 5 years, 18% at 10 years and 24% at 15 years (Fig. 1). The overall average risk of progression was approximately 1.5% per year. It must be noted that patients were at risk for progression throughout the entire period of observation.

The physician must realize that the rates of death due to cardiovascular or cerebrovascular diseases and non-lymphoid or plasmacytic malignancies are much higher – 31% at 5 years, 52% at 10 years and 65% at 15 years. Obviously this is much greater than the rates of progression to lymphoplasmacytic malignancies which were 8% at 5 years, 12% at 10 years and 15% at 15 years (Fig. 2).

On multivariate analysis, the size of the serum M-protein at time of recognition of MGUS ($p=.03$) and the serum albumin value ($p=.01$) were the only risk factors for progression. In this series, the reduction of uninvolved (IgG and/or IgA) immunoglobulins or a monoclonal light chain in the urine were not statistically significant risk factors. The risk of progression to lymphoma or a related malignancy 10 years after recognition of MGUS was 14% for an initial IgM M-protein value of 0.5 g/dL or less but 41% for persons with an initial IgM protein of 2.5 g/dL (Fig. 3).

Smoldering Waldenström's Macroglobulinemia (SWM)

Again, virtually all patients with symptomatic WM have passed through an IgM MGUS and then SWM, but many of these are not recognized. In a cohort of 452 patients with WM at the Mayo Clinic, 19% had had SWM. In the majority of excluded patients ($n=39$), either the bone marrow examination was not performed within 30 days of SWM or the biopsy results were unavailable for review; 5 patients were excluded because of biclonal gammopathy (monoclonal IgM plus IgG or IgA). The 48 documented patients with SWM had a median age of 63 years while 2% were younger than 40 years of age and two-thirds were male. A palpable liver and/or spleen was noted in 20% while 10% had asymptomatic lymphadenopathy. All patients with a hemoglobin < 10 g/dL was unrelated to the lymphoplasmacytic infiltration and a more likely cause was evident. Twenty-seven percent of the SWM patients had a bone marrow lymphoplasmacytic infiltration 50%. At diagnosis of SWM, the serum monoclonal protein ranged from 1.5 g/dL to 5.2 g/dL (median 3.3 g/dL). Seventy-five percent had an IgM monoclonal kappa protein. IgG and/or IgA was reduced in 47%. A urine monoclonal protein > 200 mg/24 hours was found in 5 patients. The median serum albumin value was 3.6 g/dL (2.5 g/dL to 4.3 g/dL). The serum albumin was < 3 g/dL in 10%. The bone marrow aspirate and/or biopsy lymphoplasmacytic infiltration ranged from 3% to 80% (median 30%).

Seventy-one percent progressed to symptomatic WM requiring chemotherapy, 1 to AL amyloidosis and 1 to lymphoma during a median follow-up of 15.4 years. The relative risk of progression was increased 8,034-fold for the entire cohort whereas one would expect 0.004 cases of WM on the basis of the SEER registry in Iowa.

The cumulative probability of progressing to symptomatic WM requiring therapy, AL amyloidosis or lymphoma was 6% at 1 year, 39% at 3 years, 59% at 5 years and 68% at 10

years (Fig. 4). The cumulative probability of progression was 12% per year for the first 5 years and then 2% per year for the next 5 years.

Significant risk factors for progression consisted of the percentage of bone marrow lymphoplasmacytic infiltration, size of the serum monoclonal protein, hemoglobin level and presence of IgA reduction (Table 2). The most important risk factor for progression was the percentage of lymphoplasmacytic infiltration of the bone marrow. Both the size of the serum M-protein and the hemoglobin level contributed significantly to a model already containing the percentage of lymphoplasmacytic bone marrow cells.

Ninety-two percent of 13 patients who had 50% or more lymphoplasmacytic infiltration in the bone marrow at diagnosis progressed during the first 5 years of follow-up while 46% of those with a bone marrow containing < 50% lymphoplasmacytic cells progressed ($p=0.001$) during the same time (Fig. 5). At five years follow-up, 61% of patients with an M-protein 3 g/dL and 10% or more bone marrow lymphoplasmacytic infiltration progressed. The median level of lymphoplasmacytic infiltration in the bone marrow was 15% in the 12 patients who did not progress during follow-up.

During follow-up 75% of the 48 patients with SWM died. The overall survival of the 48 SWM patients was 83% at 5 years and 50% at 9.6 years. Seven patients died of cardiovascular or cerebrovascular disease or other unrelated disorders before developing WM or a related disorder. The median survival after progression to symptomatic WM was 5.1 years. Only 5 SWM patients were alive and at risk for progression after being followed for 14-24.6 years.

Waldenström's Macroglobulinemia

The diagnosis of WM requires the presence of a monoclonal IgM monoclonal protein of any size and a bone marrow containing 10% of small leukocytes with plasmacytoid differentiation (lymphoplasmacytic lymphoma). The infiltration has the same immunophenotype as IgM MGUS and SWM. The median age is approximately 70 years with a male/female predominance of 2:1. Constitutional symptoms consisting of weakness, fatigue, weight loss and night sweats, easy bleeding from the oronasal area and easy bruising are not uncommon. Blurring of vision may occur from hyperviscosity. Recurrent infections may be seen. Neurologic abnormalities are seen initially in approximately 20% of patients. Peripheral neuropathy is common and usually begins in the lower extremities and is slowly progressive. Cranial nerve palsies as well as infiltration of the central nervous system by lymphoplasmacytic cells rarely occur. Hyperviscosity may produce headache, blurred vision, vertigo, ataxia, diplopia, seizures and even altered consciousness or coma.

Renal insufficiency is uncommon despite the deposition of IgM on the basement membrane. Nephrotic syndrome is rare unless systemic AL amyloidosis is also present. Diffuse pulmonary infiltrates, masses or pleural effusion may be seen. Infiltration of the skin by lymphoplasmacytoid leukocytes are rarely observed.

Anemia is found in the majority of patients. Occasionally an acquired hemolytic anemia with a positive Coombs test may occur. The plasma volume is increased and this contributes

to the low hemoglobin and hematocrit levels. Serum protein electrophoresis reveals a sharp, narrow spike or dense band usually migrating in the gamma area. Immunofixation must be performed to confirm the presence of a monoclonal protein and to determine its type. Approximately three-fourths of WM patients have an IgM kappa monoclonal protein. The quantitative value of IgM on nephelometry is often 1-2 g/dL more than the measurement of the serum spike. IgG and IgA are reduced frequently. The bone marrow aspirate is often hypocellular but the biopsy is usually hypercellular with an extensive infiltration of clonal lymphoid and plasmacytoid cells. Mast cells are frequently increased in the marrow.

WM must be differentiated from IgM MGUS and SWM as well as multiple myeloma, chronic lymphocytic leukemia, mantle cell, marginal zone and MALT lymphoma.

Prognostic Factors

Facon et al., described prescribed prognostic factors for survival in 167 patients with WM from a single institution.(8) The following were the most important adverse prognostic factors for survival: neutrophils $< 1.7 \times 10^9/L$, age > 60 years and a hemoglobin concentration of < 10 g/dL. The median survival of these patients was 5 years. Gobbi et al., found with multivariate analysis that age > 70 years, hemoglobin < 9 g/dL and the presence of weight loss or cryoglobulinemia were the most important prognostic features.(9) In another report, Morel et al., stated that age > 65 years, serum albumin < 4 g/dL and the presence of 1 or more cytopenias were major risk factors concerning survival.(10) The OS at 5 years was 87% in those with 1 risk factor, 62% in those with 2 adverse risk factors and only 25% in patients with 3 adverse risk factors. Dhodapkar et al.(11), utilized serum beta-2 microglobulin, hemoglobin value and serum IgM concentrations to separate WM patients into low risk who had $\beta 2$ -microglobulin < 3 mg/L and hemoglobin > 12 g/dL while median risk patients were defined as $\beta 2$ -microglobulin < 3 mg/L and hemoglobin < 12 g/dL or $\beta 2$ -microglobulin > 3 mg/L and serum IgM < 4 g/dL whereas high risk patients had $\beta 2$ -microglobulin > 3 mg/L and IgM > 4 g/dL. Those patients categorized as having low risk had a 5-year OS of 87%, median risk 63% and 53% while high risk patient had a 21% 5-year survival. An elevated serum lactate dehydrogenase (LDH) was an additional poor prognostic factor at 10 years follow-up.

Morel et al., developed an International Prognostic Staging System for WM (IPSS WM) based upon 587 patients with WM from 7 international institutions.(12) The significant adverse features consisted of age > 65 years, hemoglobin < 11.5 g/dL, platelets $< 100 \times 10^9/L$, $\beta 2$ -microglobulin > 3 mg/L and serum IgM > 7 g/dL. Patients considered to have low-risk disease were characterized by age < 65 years and having only 0 or 1 risk factors. Those classified as high risk had > 2 risk factors and accounted for 35% of patients while the intermediate group had 2 risk factors or were older than 65 years and accounted for 38%. Overall survival was 87, 68 and 36% respectively in the low, intermediate and high-risk groups. Gender, presence of B symptoms, IgM value, performance status, presence of hyperviscosity, bone marrow infiltration and cytogenetic changes have also been reported as risk factors by other investigators.

When Should One Treat Patients with WM?

Patients with severe constitutional symptoms such as daily fever, drenching night sweats or marked weight loss require immediate therapy. One must be certain that the constitutional symptoms are due to WM and not another entity. Patients with anemia that produces dyspnea, angina or marked fatigue should also begin therapy. Immediate plasmapheresis is indicated if the patient has evidence of hyperviscosity such as oronasal bleeding, blurred vision or neurologic symptoms. It must be emphasized that elevation of serum viscosity without symptoms or eye ground changes characteristic of hyperviscosity is not an indication for plasmapheresis. Large lymphadenopathy producing symptoms such as a “bull” neck requires therapy. Hepatosplenomegaly may sometimes produce abdominal fullness, discomfort or pain and require treatment. If the adenopathy is retroperitoneal it is usually asymptomatic and does not require specific therapy. One must emphasize that the size of the IgM spike in serum protein electrophoresis or the IgM level are not indications for therapy unless other features of WM are present.

In addition, patients with a high percentage of infiltration of the bone marrow biopsy with clonal lymphocytes and plasma cells may be asymptomatic and these patients should continue to be observed. Approximately 10% of patients with smoldering WM, followed for nearly a decade, remain asymptomatic and do not require therapy.(6) Delaying therapy until development of symptoms does not adversely affect survival in SWM.(7) We must adhere to the sage advice of Jan Waldenström when he stated “let well alone”(13) Clinicians must resist the temptation to initiate therapy solely to improve the abnormal laboratory values in the patient because WM remains incurable. Waldenström emphasized the need to listen to the symptoms of the patient and to perform a complete physical examination and to avoid therapy for mild symptoms. We must not forget that patients do not require treatment simply because of a large monoclonal IgM serum protein or marked infiltration of the bone marrow with lymphocytes and plasma cells. Waldenström emphasized that if the patient was able to state on his tombstone the words “Vixit, dum vixit, laetus” (He lived happily as long as he lived) from the Swedish poet, Stiernhielm the physician has indeed, succeeded in improving the quality of life of the patient. In short, as in many diseases, the physician is faced with the challenge of not treating the patient too early nor delaying therapy in the presence of appropriate indications for treatment.

Follow-up of the “Watch-and-Wait” Patients

Follow-up is recommended in 3-4 months in patients who present with the findings of SWM. If stable initially, the interval of follow-up can usually be extended to 6-month intervals. Annual follow-up is reasonable if the patient’s clinical and laboratory findings remain stable. The physician must emphasize that the patient contact their physician in the event of any new symptoms or change in their condition.

Despite the many advances in the treatment of hematologic malignancies, there is no single standard therapy for symptomatic WM. Prospective trials are important and should be utilized if at all possible. This is the only way that one can determine the efficacy of various agents or combinations thereof. Few prospective randomized studies have been performed.

In summary, a detailed history, complete physical examination including funduscopy (preferably with dilation of the pupil by an ophthalmologist) to evaluate retinal vein engorgement as well as hemorrhages and exudates and papilledema must be done. We recommend the use of densitometry in determining the IgM level. Nephelometry may also be used. It is essential that the level of IgM on nephelometry should not be directly compared with the results of densitometry. Patients who have a rapidly rising IgM level or have an increase in signs or symptoms of WM may be started on therapy. Patients with hemoglobin values < 10 g/dL and/or a platelet level $< 100 \times 10^9/L$ that are due to the disease are additional indications for beginning therapy. Treatment is also warranted if bulky lymphadenopathy or symptomatic organomegaly is present. Patients with recurrent high fever, drenching night sweats, significant weight loss or progressive fatigue also warrant therapy. Patients who have symptomatic hyperviscosity, severe symptomatic neuropathy, systemic amyloidosis related to WM or symptomatic cryoglobulinemia should also be treated. Most importantly, immediate plasmapheresis is required for symptomatic hyperviscosity.

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Practice Points and Research Agenda

- Waldenström's Macroglobulinemia (WM) must be differentiated from Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Waldenström's Macroglobulinemia (SWM) which are intermediate lymphoplasmacytic proliferative disorders and precede WM in all instances.
- Waldenström's Macroglobulinemia should not be treated until constitutional symptoms (weakness, fatigue, fever, night sweats or weight loss), symptomatic hepatosplenomegaly or lymphadenopathy, hemoglobin < 10 g/dL, or platelets $< 100 \times 10^9/L$, symptomatic hyperviscosity, severe symptomatic neuropathy, systemic amyloidosis or symptomatic cryoglobulinemia are present.
- Initial therapy consists of rituximab, cyclophosphamide and dexamethasone, rituximab, bortezomib and dexamethasone or Rituxan plus bendamustine. Additional therapies consist of ibrutinib, fludarabine, Cladribine or chlorambucil. Prospective clinical trials are needed.

Fig. 1.

Probability of progression in 213 patients. Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Curve shows probability of progression of MGUS to lymphoma, Waldenström macroglobulinemia, primary amyloidosis, or chronic lymphocytic leukemia. Bars show 95% confidence intervals. Numbers at bottom of the horizontal axis are numbers of patients at risk at each interval. This research was originally published in *Blood*. Kyle RA et al., Long-Term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood*. 2003;Vol 102:3759-3764. © the American Society of Hematology.

Fig. 2. Competitive model in 213 patients. Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Upper curve shows probability of dying of nonlymphoid diseases. Lower curve shows probability of progression to lymphoma or a related disorder. This research was originally published in Blood. Kyle RA et al., Long-Term follow-up of IgM monoclonal gammopathy of undetermined significance. Blood. 2003;Vol 102:3759-3764. © the American Society of Hematology.

Fig. 3.

Relative risk of disease progression in 213 patients. Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class as diagnosed from 1960 through 1994. Risk is by monoclonal protein value at diagnosis. Error bars show 95% CI. This research was originally published in *Blood*. Kyle RA et al., Long-Term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood*. 2003;Vol 102:3759-3764. © the American Society of Hematology.

Fig. 4.

Cumulative probability of progression to symptomatic WM requiring therapy, amyloidosis or lymphoma in the cohort of 48 patients with SWM. This research was originally published in *Blood*. Kyle RA et al., Progression in smoldering Waldenström macroglobulinemia: long-term results. *Blood*. 2012;Vol 119:4462-4466. © the American Society of Hematology.

Fig. 5. Probability of progression to symptomatic WM requiring therapy on the basis of lymphoplasmacytic bone marrow infiltration. This research was originally published in *Blood*. Kyle RA et al., Progression in smoldering Waldenström macroglobulinemia: long-term results. *Blood*. 2012;Vol 119:4462-4466. © the American Society of Hematology.

Table 1

Observed and expected progression and standardized incidence rates among 213 patients with IgM monoclonal gammopathy of undetermined significance

Disease progression	Observed	Expected *	SIR	95% CI
Non-Hodgkin lymphoma	17	1.1	14.8	8.6-23.7
Amyloidosis	3	0.18	16.3	3.4-47.5
Macroglobulinemia	6	0.02	262	96.0-569.5
Chronic lymphocytic leukemia	3	0.53	5.7	1.2-16.5
Total group	29	1.83	15.9	11.0-22.8

MGUS was diagnosed between 1960 and 1994 in patients in southeastern Minnesota.

SIR indicates standardized incidence rate; 95% CI, 95% confidence interval.

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* Iowa SEER Registry.

Table 2

Risk factors for progression to treatment among 48 patients with Smoldering Waldenström's Macroglobulinemia (SWM)

Multivariate Model		
	Hazard Ratio	P Value
Bone marrow lymphoplasmacytic cells	1.31 (1.1-1.5)	< .001
Hemoglobin value	0.7 (0.5-0.9)	.002
Serum M Protein value	2.1 (1.3-3.5)	.003
IgA reduction	2.4 (1.1-5.4)	.036

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