

Prognostic Markers and Criteria to Initiate Therapy in Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations From the Second International Workshop on Waldenstrom's Macroglobulinemia

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This presentation represents consensus recommendations on prognostic markers and criteria to initiate therapy in patients with Waldenstrom's macroglobulinemia (WM), which were prepared in conjunction with the Second International Workshop held in Athens, Greece during September 2002. The panel recommended that initiation of therapy should not be based on the IgM level per se since this may not correlate with the clinical manifestations of WM. The consensus panel agreed that initiation of therapy was appropriate for patients with constitutional symptoms such as recurrent fever, night sweats, fatigue due to anemia, or weight loss. The presence of progressive, symptomatic lymphadenopathy or splenomegaly provide additional reasons to begin therapy. The presence of anemia with a hemoglobin value of ≤ 10 g/dL or a platelet count $< 100 \times 10^9/L$ due to marrow infiltration also justifies treatment. Certain complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia may also be indications for therapy. Recommendations for follow-up of watch-and-wait patients are that those with monoclonal gammopathy of undetermined significance (MGUS) should have serum protein electrophoresis repeated each year. Patients with asymptomatic (smoldering) macroglobulinemia should be evaluated every 6 months. Regarding prognostic markers, hemoglobin and β_2 -microglobulin levels at diagnosis are important

prognostic markers in WM: they influence the timing of treatment and survival. Age is a consistently important prognostic factor for survival. However, the panel felt that current data are inadequate to support the use of any prognostic marker to select the timing and type of therapy, and called for studies on the application of prognostic markers in WM.

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WALDENSTROM'S macroglobulinemia (WM) is characterized by the proliferation of B lymphocytes that produce an IgM monoclonal protein. This broad definition includes persons with monoclonal gammopathy of undetermined significance (MGUS) of the IgM type, lymphoma, primary amyloidosis (AL), chronic lymphocytic leukemia (CLL), and WM. Previously, WM had been defined as a malignant B-cell proliferative disorder with an IgM monoclonal protein level of 3 g/dL or more. However, many patients with bone marrow or nodal infiltration by monoclonal lymphocytes or plasmacytoid lymphocytes producing anemia, constitutional symptoms, hepatosplenomegaly, and lymphadenopathy require treatment but do not have a monoclonal protein value > 3 g/dL. Furthermore, there is no difference in survival or most clinical features based on the level of monoclonal protein, except for a greater likelihood of hyperviscosity with higher IgM levels. Consequently, from a treatment perspective, there is no rationale for separating patients based on the level of monoclonal IgM.

Patients may present with a high monoclonal protein level (> 3 g/dL) and have a significant infiltration of the bone marrow with lymphocytes and plasma cells but have no constitutional symptoms, significant hepatosplenomegaly, or lymphadenopathy. They also have little or no anemia. Biologically these patients have an MGUS but their serum M-protein and bone marrow involvement is much greater than one sees in MGUS. These patients are classified as having smoldering or asymptomatic macroglobulinemia. Patients

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Table 1. Multivariate Analyses of Survival in WM With Prognostic Scoring System

Study	Prognostic Factors	No. of Groups	Survival
Gobbi et al ⁵	Hb < 9 g/dL	0-1 prognostic factor	Median survival, 48 mo
	Age > 70 yr Weight loss	2-4 prognostic factors	Median survival, 80 mo
Morel et al ⁷	Cryoglobulinemia	0-1 prognostic factor	5-yr survival rate, 87%
	Age ≥ 65 yr Albumin < 4 g/dL	2 prognostic factors	5-yr survival rate, 62%
Dhodakpar et al ⁸	Total no. of cytopenias: Hb < 12 g/dL Platelets < 150 × 10 ⁹ /L WBC count < 4 × 10 ⁹ /L	3-4 prognostic factors	5-yr survival rate, 25%
	β ₂ -M ≥ 3mg/L	β ₂ -M < 3 mg/L + Hb ≥ 12 g/dL	5-yr survival rate, 87%
	Hb < 12 g/dL	β ₂ -M < 3 mg/L + Hb < 12 g/dL	5-yr survival rate, 63%
	IgM < 4 g/dL	β ₂ -M ≥ 3 mg/L + IgM ≥ 4 g/dL β ₂ -M ≥ 3 mg/L + IgM < 4 g/dL	5-yr survival rate, 53% 5-yr survival, 21%

Abbreviations: Hb, hemoglobin; WBC, white blood cell; β₂-M, β₂-microglobulin.

with asymptomatic monoclonal IgM < 3 g/dL, hemoglobin > 12 g/dL, and absence of symptomatic lymphadenopathy or splenomegaly may be classified as having IgM MGUS. This condition is discovered by chance and is the most common diagnosis among individuals with a monoclonal IgM. Differentiation of IgM-MGUS from asymptomatic WM may be difficult. Nevertheless, both are followed without treatment. Some patients may have symptoms due to the biological effects of the monoclonal IgM protein. Such patients may have symptomatic peripheral neuropathy, cryoglobulinemia, cold agglutinin disease, or AL. These patients need treatment to control complications from the monoclonal IgM produced by a small clone of lymphocytes.

Patients with asymptomatic or smoldering macroglobulinemia should be recognized and not treated because they may remain stable for many years. In this situation the advice of Jan Waldenström "let well alone" must be kept in mind.¹ He emphasized the temptation to begin chemotherapy in order to obtain normal values in the patient. Waldenström also emphasized the need to listen to the patient and to perform a careful physical examination and to avoid treatment of a symptom. These patients should not be treated simply on the basis of a laboratory abnormality such as a large monoclonal serum protein or on the basis of a pathology report indicating significant infiltration of the bone marrow with lymphoid cells. Walden-

ström also emphasized the importance of quality of life. If the patient is able to state on his tombstone the words of the great Swedish poet, Stiernhielm, "*Vixit, dum vixit, laetus*" (he lived happily as long as he lived), the physician has succeeded in improving the quality of life of the patient.

The median survival of patients with WM averages 5 years, but at least 20% of patients survive for more than 10 years, and 10% to 20% die of unrelated causes.²⁻⁴ Because WM is an uncommon disorder, relatively few studies have defined prognostic factors in large patient populations. Although several studies have analyzed prognostic factors for survival in WM,³⁻¹³ only three multivariate analyses have yielded prognostic scoring systems based on large series^{6,8,9} (Table 1). In the Italian study, the criteria that discriminated two prognostically different populations were age, weight loss, hemoglobin level, and cryoglobulinemia.⁶ A recent multivariate analysis of the overall survival on 215 patients with a longer follow-up found four prognostic markers: β₂-microglobulin, hemoglobin, albumin, and age.⁷ In the French study, a combination of age, albumin, and blood cell counts provided a simple prognostic model for survival⁸: with these simple parameters, patients were stratified into three groups at low, intermediate, and high risk of death, with 5-year survival probabilities of 92%, 63%, and 27%, respectively. In the Southwest Oncology Group (SWOG) study, a serum β₂-microglobulin level higher than

3 mg/L, a hemoglobin level below 12 g/dL, and a serum IgM level below 4 g/dL were significant adverse prognostic factors for survival.⁹ A staging system using these variables identified four distinct subsets of patients with estimated 5-year survival rates of 87%, 64%, 53%, and 12%.

Many other prognostic factors have been described in smaller series of patients, such as gender, B symptoms, the IgM level, performance status, hyperviscosity, bone marrow infiltration pattern, and cytogenetic abnormalities,³⁻¹³ but patient numbers were small, follow-up was frequently short, and multivariate analysis was often not performed. Survival appears to be better in patients who respond to therapy than in those with resistant disease. The response can therefore be considered as a potential surrogate of survival but not as a prognostic factor.^{5,14,15} In contrast, it remains to be shown whether complete remission confers a survival benefit.

IDENTIFICATION AND RECOMMENDATIONS FOR THE USE OF PROGNOSTIC MARKERS IN WM

The expert panel separated factors used to determine the need for initiation of treatment from factors predictive of survival.

Factors Identifying Patients Likely to Require Treatment in the Short Term

Hemoglobin and β_2 -microglobulin levels at diagnosis are important factors for predicting whether treatment will be required in the relative short term. Additional studies though are needed to validate if these, as well as other prognostic markers, can be used to determine initiation and selection of therapy.

Discussion

In three studies^{3,9,16} normal serum β_2 -microglobulin level and a hemoglobin level of at least 12 g/dL,⁹ 12.5 g/dL,³ or 11.5 g/dL¹⁶ at diagnosis identified a subset of patients who were less likely to require therapy in a short term. Hemoglobin level < 12.5 g/dL was also shown to predict transformation into active disease requiring treatment.¹⁷

Factors Predictive of Overall Survival

Age is consistently an important prognostic factor, with cut-off values ranging from > 60 years,^{5,7} to > 65 years,^{3,8,10} or > 70 years.^{6,9} However, this

factor is impacted by unrelated diseases and could disappear as a factor in analyses using cause-specific survival.¹⁶ Anemia, which reflects both marrow infiltration and the serum level of monoclonal protein, was an adverse prognostic factor: hemoglobin level is a strong predictor of the survival rate in all published series: hemoglobin < 10.5 g/dL,² < 9 g/dL,⁵ < 10 g/dL,⁶ and < 12 g/dL.^{8,9} Cytopenia is also regularly identified as a significant survival predictor. However, the precise levels of cytopenia with prognostic significance remain to be determined. Some series have identified the platelet count (< 150×10^9 /L,⁸ < 120×10^9 /L⁶) and the white blood cell count (< 4×10^9 /L⁸) as independent prognostic factors. The number of types of cytopenia in a given patient has been proposed as a strong prognostic factor.^{8,10} Serum albumin level was correlated with survival in two main WM populations by multivariate analysis,^{7,8} but it was not identified in other studies.^{3,10} High β_2 -microglobulin values were linked to poor survival in all of the studies in which they were analyzed.^{3,7,9} A precise cut-off value for this parameter needs to be determined in future studies.

Discussion

Hemoglobin and β_2 -microglobulin levels at diagnosis are important prognostic markers in WM: they appear to influence the timing of treatment and survival. However, the precise levels of hemoglobin and β_2 -microglobulin with prognostic significance remain to be determined. Age is consistently an important prognostic factor for survival. Serum albumin level is correlated with survival in two main WM populations. Other parameters (other cytopenias; bone marrow pathological findings; hyperviscosity; performance status; Morel, Dhodapkar, and Gobbi scores) and biological data (IgM level and cytogenetics) need to be validated in prospective studies. Additional studies are needed to determine whether these and other prognostic markers can be used to decide on the initiation and selection of therapy.

Should Prognostic Markers Be Used in the Decision-Making Process for Recommending Initiation and Type of Therapy, Including Participation in a Clinical Trial?

The panel felt that insufficient data exist at present to affirm the use of any prognostic marker

in the initiation and selection of therapy, and identified studies into the application of prognostic markers in WM as an important area of need.

CLINICAL AND LABORATORY CONSIDERATIONS FOR INITIATION OF THERAPY IN WM

The panel recommended that a thorough history, physical examination including funduscopic examination to exclude retinal vein engorgement with hemorrhaging and exudates, and papilledema and determination of a serum viscosity level determinations (if available) should be undertaken at initial examination and on follow-up examinations as needed for evaluation of hyperviscosity.

The panel also considered that the use of densitometry should be adopted to determine IgM levels for serial evaluations since nephelometry remains unreliable and shows large intralaboratory as well as interlaboratory variation.

The panel considered that initiation of therapy should not be based on consideration of IgM levels per se, since these may not correlate with clinical manifestations of WM. However, initiation of therapy is reasonable for those patients who demonstrate rising IgM levels with progressive signs or symptoms of disease.

The panel considered that initiation of therapy was appropriate for patients who demonstrated a hemoglobin level of ≤ 10 g/dL and/or platelet count of $< 100 \times 10^9$ /L that were attributable to disease, bulky adenopathy, or organomegaly, or any other disease-related complaints that were serious enough to warrant therapy including recurrent fever, night sweats, weight loss, fatigue, or symptomatic manifestations associated with WM including hyperviscosity, symptomatic neuropathies, nephropathy, amyloidosis, symptomatic cryoglobulinemia, or evidence of disease transformation. In the absence of the above, close observation of patients was reasonable.

The panel considered that patients who demonstrated signs or symptoms suggestive of symptomatic hyperviscosity should be considered for immediate plasmapheresis, and initiation of chemotherapy as soon as possible.

Discussion

Constitutional symptoms such as recurrent fever, night sweats, fatigue due to anemia, or weight loss are indications for therapy. The presence of

progressive, symptomatic lymphadenopathy or splenomegaly provide additional reasons to begin therapy. Finally, the presence of anemia with a hemoglobin value ≤ 10 g/dL or a platelet count $< 100 \times 10^9$ /L due to marrow infiltration also justifies treatment. Certain complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency (rare), or symptomatic cryoglobulinemia may also be indications for therapy. Initiation of therapy should not be based on the IgM level per se, since this may not correlate with the clinical manifestations of WM. The use of densitometry should be adopted to define IgM levels for serial evaluation because nephelometry may produce erroneous elevations and is associated with considerable interlaboratory and intralaboratory variation. Initiation of therapy is reasonable for those patients who demonstrate rising IgM levels associated with progressive signs or symptoms of disease. Patients who demonstrate signs or symptoms suggestive of symptomatic hyperviscosity should be considered for immediate plasmapheresis and initiation of chemotherapy.

An IgM level > 3 g/dL places patients at higher risk for hyperviscosity and requires that a thorough history be obtained for evidence of oronasal bleeding, blurred vision, headache, dizziness, vertigo, ataxia, encephalopathy, or altered consciousness. Funduscopic examination is necessary to detect signs of hyperviscosity such as venous dilatation, "sausage formation" hemorrhages, and exudates. Measurement of serum viscosity should be performed if available. The correlation between serum viscosity levels and symptoms is often poor from patient to patient. However, the serum viscosity level correlates well with clinical signs and symptoms in the same patient. Most patients with a serum viscosity < 4 cp will not have symptoms of hyperviscosity (normal = 1.8 cp).

RECOMMENDATIONS FOR FOLLOW-UP OF WATCH-AND-WAIT PATIENTS

For asymptomatic (smoldering) WM patients, close interval follow-up is recommended (every 3 to 6 months). For patients with the diagnosis of IgM-MGUS, serum IgM levels should be rechecked at 3 months, and if stable, annual follow-up thereafter would be considered reasonable. The patient should be advised to return to the

physician in the event of any symptoms or untoward problems.

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