Original article

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Survival and prognostic factors after initiation of treatment in Waldenstrom's macroglobulinemia

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Backgroud: Waldenstrom's macroglobulinemia (WM) is an unusual lymphoplasmacytoid lymphoma characterized by the presence of a serum monoclonal immunoglobulin M. Although several studies have evaluated possible prognostic factors of this disease, few have focused on the survival and prognosis of symptomatic patients after the initiation of treatment.

Patients and methods: Our study included 122 previously untreated patients with a median age of 67 years who required systemic treatment. Multiple variables were analyzed for their prognostic value on survival after initiation of treatment using univariate and Cox regression multivariate analysis.

Results: The median overall survival was 106 months. Pretreatment factors associated with shorter survival were age ≥65 years, splenomegaly, B-symptoms (weight loss, fever or night sweats), hemoglobin <10 g/dl, platelets $<100 \times 10^6$/dl, albumin <3.5 g/dl and bone marrow lymphoplasmacytic infiltrate ≥50%. In the multivariate analysis, the two variables with independent prognostic value were age ≥65 years and hemoglobin <10 g/dl. Furthermore, we were able to divide our patients into three risk groups based on the presence of two, one or none of these two adverse prognostic factors. The median survival times in the high-, intermediate- and low-risk groups were 46 months, 107 months and 172 months, respectively (P <0.0001).

Discussion: Our findings suggest that advanced age and anemia appear to be the two dominant prognostic factors for survival after initiation of treatment in patients with WM. These two readily available parameters can stratify the patients into three distinct subgroups and may help the selection of appropriate treatment.

Key words: prognosis, survival, treatment, Waldenstrom's macroglobulinemia

Introduction

Waldenstrom's macroglobulinemia (WM) is a low-grade lymphoplasmacytoid lymphoma characterized by the production of monoclonal immunoglobulin M (IgM). According to the Revised European American Lymphoma Classification of lymphoid neoplasms, the diagnosis of WM is established by the presence of monoclonal IgM in the serum and infiltration of bone marrow by a proliferation of small lymphocytes, plasmacytoid lymphocytes and plasma cells [1, 2].

WM is an infrequent disease that affects ~1500 Americans each year; it is ~10–20% as common as multiple myeloma. Most patients with WM present with symptoms, signs or other complications that require prompt initiation of systemic treatment in order to reduce the proliferation of the malignant clone. However, several patients are diagnosed by chance and do not have symptoms, anemia, significant hepatosplenomegaly or lymphadenopathy, or complications associated with the presence of monoclonal IgM. Such asymptomatic patients are followed without any treatment for several months or years until there is evidence of disease progression [3].

WM is a relatively indolent disease with a median survival of 5–10 years in different series. Several studies have evaluated clinical and laboratory parameters associated with shorter or longer survival of patients with WM [4–11]. Most of these studies have included a mixed population of patients consisting of symptomatic patients who received treatment at diagnosis and of asymptomatic patients who required treatment several months or years after diagnosis. Thus, in several studies it was not clear which variables were predictive specifically for the symptomatic patients who needed treatment. We thus designed a retrospective study that included previously untreated patients who required systemic treatment, and we focused on their survival and prognosis after the initiation of treatment.

Patients and methods

Between January 1985 and June 2001, 122 patients with WM were identified who had lymphoplasmacytic infiltration of their bone marrow along with a serum monoclonal IgM, and who required systemic treatment. Patients with indolent WM were not included.

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A database was constructed, which included the following parameters: age, gender, presence of B-symptoms, splenomegaly, lymphadenopathy, hyperviscosity, cryoglobulinemia, cold agglutinin anemia, amyloidosis, neuropathy, hypercalcemia, bone lesions, or other extranodal involvement. Other parameters included complete blood counts, liver and renal function tests, serum monoclonal protein, serum albumin, quantitation of serum immunoglobulins, serum β2-microglobulin, type of light chain, Bence Jones proteinuria, serum LDH, and percentage and pattern of bone marrow infiltration. Moreover, the primary indication of the need to start treatment, the type of primary treatment and the response to treatment were coded.

Complete response was defined as the disappearance of the monoclonal protein by immunofixation, resolution of lymphadenopathy and organomegaly, and <20% normal appearing lymphocytes in the bone marrow. Partial response was defined as ≥50% reduction of serum monoclonal protein concentration for at least 2 months along with ≥50% reduction of tumor infiltrate at all involved sites. The disease was considered stable when the reduction of serum monoclonal protein ranged from 0% to <50% without an increase in lymphadenopathy and organomegaly, and without evidence of additional disease complications. Patients were rated as having progressive disease when they did not meet the criteria for response or stable disease.

Survival was considered from the first day of treatment to the time of death or last follow-up. Several clinical and laboratory characteristics were considered for analysis concerning their individual and simultaneous effects on survival. These parameters were adapted from previous series that evaluated prognostic factors in Waldenstrom's macroglobulinemia and included: age, gender, hyperviscosity, B-symptoms (weight loss, fever or night sweats), splenomegaly, lyphadenopathy, levels of monoclonal protein, type of light chain, anemia, thrombocytopenia, leukopenia, hypoalbuminemia and bone marrow infiltration. Survival curves were plotted using the Kaplan–Meier method [12]. Statistical comparisons between actuarial survival curves were based on log-rank and Wilcoxon tests [13, 14]. The cut-off point of each variable was selected by comparison of the alternative cut-off points based on the minimum *P*-value method [15]. Variables considered for possible inclusion in the Cox analysis were those for which there was a significant association in univariate analysis ($P < 0.05$) or for which previous studies had suggested a possible association [16]. The stepwise regression procedure was stopped when the *P* value for entering an additional factor was >0.01. The model was tested both by expressing values in a continuous way (continuous variables) and by grouping them into categories (dichotomous variables). Since β2-microglobulin was recorded in 62 patients only, it was not included in the Cox model.

Table 1. Patients and disease features before initiation of treatment

Total number of patients (*n*)	122
Age (years)	
Median	67
Range	27–87
Males/females (*n*)	72/50
Percentage with light-chain:	
Kappa	73
Lambda	27
A symptoms (%)	84
B symptoms (%)	16
Palpable spleen (%)	43
Lymphadenopathy (%)	40
Hyperviscosity (%)	20
Peripheral neuropathy (%)	8
Cryoglobulinemia (%)	7
Cold agglutinin anemia (%)	3
Amyloidosis (%)	3
Anemia (%)	
Hemoglobin (Hb) <12 g/dl	82
Hb <10 g/dl	49
Thrombocytopenia (%)	
Platelet count $<150 \times 10^6$/dl	27
Platelet count $<100 \times 10^6$/dl	13
Serum monoclonal protein (g/dl)	
Median	3.42
Range	0.3–11.7
Hypoalbuminemia (%)	
Albumin <4.0 g/dl	69
Albumin <3.5 g/dl	44
Bone marrow infiltration ≥50% (%)	57

Results

Clinical and laboratory characteristics

The median age of the 122 patients was 67 years and the male to female ratio was 1.44 (Table 1). At least one-third of patients had clinical or radiological evidence of splenomegaly and of lymphadenopathy. Approximately one-fifth of patients had B-symptoms before the initiation of treatment. Hyperviscosity was prominent in 24 patients and peripheral polyneuropathy was evident in 10 patients. Symptomatic cryoglobulinemia and cold agglutinin syndrome were seen in a few patients only (Table 1). Amyloidosis was detected in four patients. Involvement of other organs was rare and included infiltration of the parotid gland, the stomach, and the subcutaneous tissue of the face (one patient each).

Serum monoclonal protein levels ranged from 0.3 to 11.7 g/dl (Table 1). Light-chain type was kappa in two-thirds of patients and light-chain proteinuria was present in 28%. The most frequent hematological abnormality was anemia, which was significant in ~50% of patients. Reduced platelet count to $<150 \times 10^6$ dl was seen in one-third of patients but thrombocytopenia (platelet count $<100 \times 10^9$ dl) was found in 13% of patients. Leukopenia [white blood cell count (WBC) $<4 \times 10^6$/dl] was detected in 16% of patients. Leukocytosis (WBC $>10 \times 10^6$/dl) was found in 15% and blood lymphocyte count $\geq 5 \times 10^6$/dl in 10%. Based on the inclusion criteria of our study, all patients had bone marrow involvement. Extensive infiltration (≥50%) of the marrow by lymphocytes and lymphoplasmacytes was detected in the majority of patients. Pretreatment data on serum β2-microglobulin were available only in 62 recently diagnosed patients; serum β2-microglobulin ≥3 mg/dl was present in 32 patients (52%).

Primary reason to start treatment and response to treatment

The most common reason to indicate the need for treatment initiation was anemia (Table 2). Symptomatic hyperviscosity necessitated treatment in one-fifth of patients. Significant or

Table 2. Primary reason for initiation of treatment

Reason	Percentage of patients with condition
Anemia	34
Hyperviscosity	20
Lymphadenopathy	16
Splenomegaly	6
Rising M-protein	6
B-symptoms	6
Cryoglobulinemia	4
Neuropathy	4
Miscellaneous conditions	4

increasing lymphadenopathy and/or splenomegaly or the presence of B-symptoms were the primary cause for treatment in several patients. Ninety-five patients (78%) were treated with alkylating agents. Chlorambucil with or without prednisone was the primary treatment in 60% of patients. Some patients received primary treatment that included combinations of alkylating agents with a vinca alkaloid such as cyclophosphamide, vincristine and prednisone (CVP) (nine patients), or with a nitrosurea such as vincristine, cyclophosphamide, melphalan, carmustine and prednisone (VMCBP) (five patients). Eight patients were treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Only nine patients were treated up front with fludarabine and 19 patients received miscellaneous treatments, including rituximab in 12 patients. Overall, an objective response (complete or partial response) was documented in 58% of patients. Complete responses were rare and were seen in only five patients. There was no difference in the response rate and survival among the different regimens.

Outcome

The median overall survival of our patients from the date of initiation of treatment was 107 months [95% confidence interval (CI) 84 to 141 months] and 46 patients died. Because the majority of our patients were censored at the time of our analysis, we plotted the survival curves of 59 patients who were diagnosed from January 1985 to December 1995, i.e. for patients who had a minimum follow-up of 7 years. The median survival of this cohort of patients was 106 months (95% CI 75 to 141 months). The cause of death was related to the disease or its treatment in 77% of patients, was considered unrelated in 16% of patients, and could not be clarified in 7% of patients.

Multiple parameters were analysed for their possible prognostic impact on patient survival. The univariate analysis showed that the following factors were associated with an impaired survival: age ≥65 years, symptomatic disease, splenomegaly, hemoglobin <10 g/dl, platelets $<100 \times 10^6$/dl, albumin <3.5 g/dl and bone marrow lymphocytes ≥50% (Table 3). Other parameters that were not associated with survival included: gender, type of light chain, WBC $<4 \times 10^6$/dl, levels of monoclonal protein, hyperviscosity and lymphadenopathy. In the multivariate analysis, the two variables with independent prognostic value were the age ≥65 years and hemoglobin <10 g/dl (Table 4). Subsequently we divided our patients into three risk groups based on the presence of two, one or none of the adverse prognostic factors. As shown in Table 5, we were able to separate our patient population into three distinct risk groups with very different survival times. Approximately one-quarter of our patients were assigned to a low-risk group with a median survival of 14 years, whereas one-quarter of them, who had both adverse disease features, survived for a median of 4 years (Figure 1).

Furthermore, in our study we attempted to validate Morel's scoring system [7]. As described previously, one-half of our patients belonged to either the low- or intermediate-risk group, and the other half to the high-risk group (Table 6). There was a statistically significant difference in the survival among the three

Table 3. Clinical and laboratory parameters associated with survival on univariate analysis (log-rank test)

Variable	Median survival (months)	*P* value
Age (years)		
<65	172	
≥65	88	0.0016
A-symptoms	116	
B-symptoms	48	0.0003
Splenomegaly		
No	141	
Yes	90	0.010
Hemoglobin		
≥10 g/dl	116	
<10 g/dl	90	0.0018
Platelet count		
$\geq 100 \times 10^6$/dl	107	
$<100 \times 10^6$/dl	55	0.0131[a]
Albumin		
≥3.5 g/dl	112	
<3.5 g/dl	77	0.028
Bone marrow lymphocytes		
<50%	141	
≥50%	84	0.012

[a]Wilcoxon test (log-rank *P* value = 0.104).

Table 4. Multivariate analysis for survival

Variable	Chi-squared	*P* value	Hazard ratio (95% confidence interval)
Age ≥65 years	3.17	0.0749	1.59 (0.95–2.65)
Hb <10 g/dl	3.82	0.0506	1.67 (1.00–2.79)

Table 5. Scoring system according to hemoglobin and age

Risk	Characteristics	Percentage of patients	Median survival (months)	*P* value
Low	Hb ≥10 g/dl and age <65 years	23	172	
Intermediate	Hb <10 g/dl or age ≥65 years	45	107	<0.0001
High	Hb <10 g/dl and age ≥65 years	32	46	

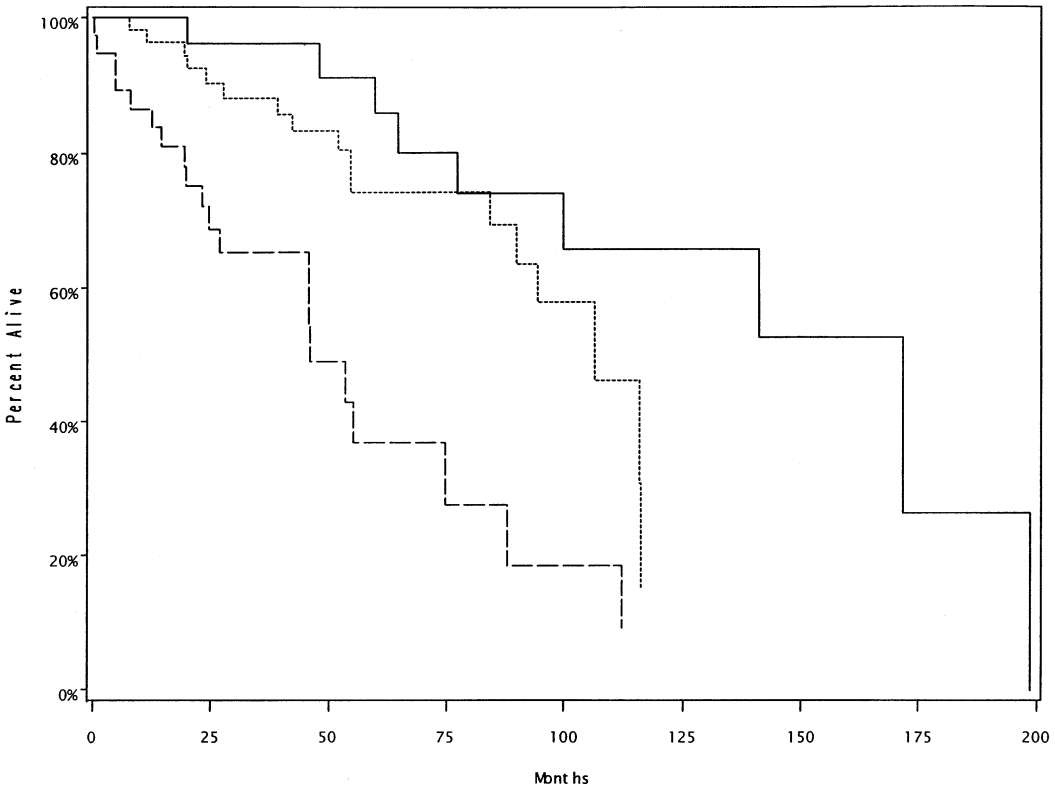

Figure 1. Survival of patients with Waldenstrom's macroglobulinemia with low risk (solid line), intermediate risk (dashed line) and high risk (dotted line), according to Table 5.

Table 6. Morel's scoring system for all patients

Risk	Percentage of patients	Median survival (months)	*P* value	5-year survival (%)
Low	17	116		75
Intermediate	29	100	0.02	87
High	54	84		50
Modified Morel's scoring system for all patients				
Low + intermediate	47	116		82
High	53	84	0.006	50

subgroups (Table 6). However, Morel's scoring system was of greater value when low- and intermediate-risk groups were grouped together and were compared with high-risk patients (Table 6; Figure 2).

Because pretreatment β2-microglobulin data were available in one-half of our patients and because the follow-up of those patients was short, β2-microglobulin was not included in the formal analysis of prognostic factors associated with survival. Nevertheless, we observed that among the 29 patients with β2-microglobulin <3 mg/dl, only four patients died with a median follow-up of 43 months. Furthermore, we performed a correlation between age and β2-microglobulin and we found that there was evidence of rising serum β2-microglobulin levels with increasing age (Spearman's $r = 25.34$; $P = 0.048$) (Figure 3).

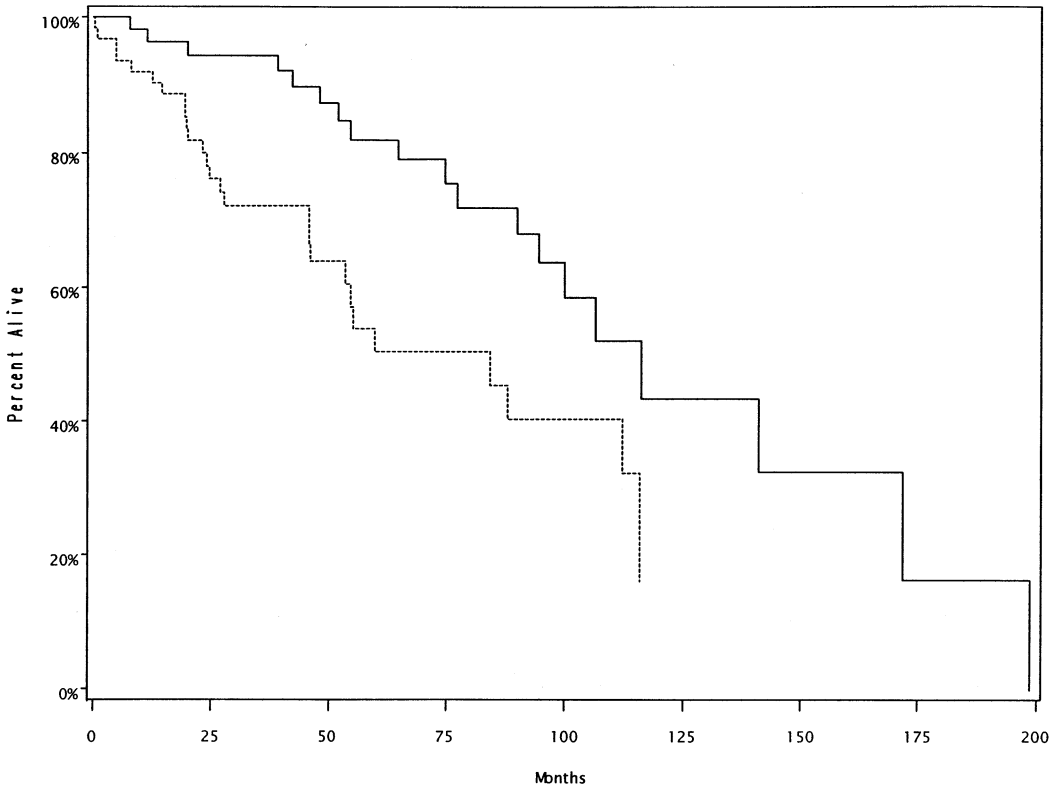

Figure 2. Survival of patients with Waldenstrom's macroglobulinemia according to a modified Morel's scoring system, as defined in Table 6 (low and intermediate, solid line; high, dotted line).

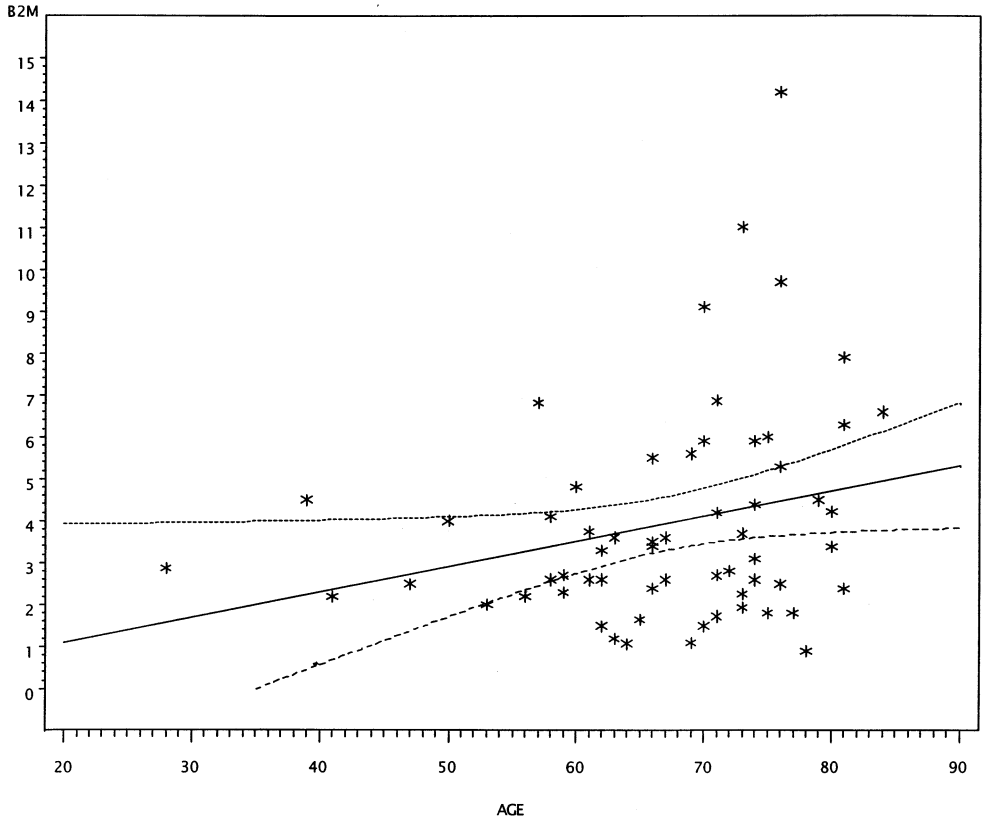

Figure 3. Serum β2-microglobulin levels rise with increasing age.

Table 7. Prognostic factors and survival in WM

Series (year)	Number of patients (% asymptomatic)	Survival	Adverse prognostic factors (multivariate)
Facon [4] (1993)	167 (30%)	From Dx: median 60 months	Age ≥60 years
			Male
			Anemia
			Neutropenia
Dimopoulos [5] (1994)	132 (0%)	From Rx: median 60 months	Not done
Gobbi [6] (1994)	144 (11%)	From Dx: median 72 months	Age ≥70 years
			Anemia
			Weight loss
			Cryoglobulinemia
Morel [7] (2000)	232 (28%)	From Dx: median 61 months	Age ≥65 years
			Low albumin
			At least one cytopenia
			At least two cytopenias
Dhodapkar [11] (2001)	118 (0%)	From Rx: 5 year, 62%	IgM <4.0 g/dl
			High β2-m
Garcia-Sanz [8] (2001)	217 (28%)	From Dx: 10 year, 55%	Without β2-m
			Age >65 years
			Anemia
			Symptoms
			With β2-m
			β2-m
			Hyperviscosity
Kyrtsonis [9] (2001)	60 (12%)	From Dx: median 108 months	Not done
Owen [10] (2001)	105 (33%)	From Dx: median 60 months	Age >60 years
			PS >1
			Platelet count $<100 \times 10^9$/l

β2-m, β2-microglobulin; Dx, diagnosis; IgM, immunoglobulin M; Rx, treatment; PS, performance status.

Discussion

We report the clinical features, response to treatment and outcome of 122 patients with WM who required initiation of treatment. Our inclusion criteria required morphological evidence of lymphoplasmacytic infiltration of the bone marrow, but we did not include a cut-off level for serum monoclonal protein, since several studies have indicated that such a restriction may not be of value [5, 11, 17]. Our analysis of 122 patients with WM requiring treatment confirmed the heterogeneity of clinical syndromes associated with this disease. While most patients required treatment due to tumor infiltration of the marrow, the spleen or the lymph nodes, in approximately one-third of patients the unique properties of monoclonal IgM were responsible for complications such as hyperviscosity, neuropathy, cryoglobulinemia and cold-agglutinin disease.

We restricted our analysis to those patients requiring treatment in order to obtain a more homogeneous patient population. Indeed, most studies reported so far have also included asymptomatic patients who were followed for several months or years without treatment, and have analyzed and compared the outcome of asymptomatic patients with that of patients requiring treatment soon after diagnosis. Among those asymptomatic patients, some individuals with IgM monoclonal gammopathy of undetermined significance might also have been included.

All published series with evaluated prognostic factors for survival in WM are listed in Table 7. In some series, up to 30% of those patients included were asymptomatic. In all but two studies a Cox regression multivariate analysis was performed. A review of these studies indicates that in most series, advanced age and anemia are the dominant adverse prognostic factors. Our data confirmed those observations. Our univariate analysis indicated that age ≥65 years, B-symptoms, splenomegaly, hemoglobin <10 g/dl, platelet count $<100 \times 10^6$/dl, albumin <3.5 g/dl and bone marrow lymphocytosis ≥50% were adverse prognostic factors. However, the stepwise regression analysis showed that the two independent variables were advanced age and anemia. By combining these two adverse prognostic factors we were able to stratify our patients

into three risk groups (high, intermediate and low risk), with significantly different median survival times of 4, 9 and 14 years, respectively.

Furthermore, in our patient population we demonstrated that Morel's scoring system may be used for prognostic stratification of patients with WM; however, we found that Morel's scoring system appeared to be more powerful when low and intermediate risk patients were grouped together and compared with those at high risk. Using this modified Morel's scoring system the patients were separated in two subgroups, with median survival times of 7 and 10 years, respectively.

Two recently published studies of prognostic factors in WM that applied a multivariate analysis have indicated that serum β2-microglobulin is a significant adverse prognostic factor. Dhodapkar et al. [11] found that elevated serum β2-microglobulin levels, anemia and low levels of serum monoclonal protein were significant adverse prognostic factors for survival. Garcia-Sanz et al. [8] indicated that high β2-microglobulin and hyperviscosity were the most significant variables. Baseline levels of serum β2-microglobulin were available in a fraction of our patient population who were recently diagnosed and in whom few events have occurred. Thus, we were not able to evaluate fully the role of this variable in our patient population. Nevertheless it appears that the 3-year survival of patients with lower levels of β2-microglobulin is better than that of patients with higher levels. The dominant prognostic value of serum β2-microglobulin in WM is in accordance with its role in multiple myeloma and chronic lymphocytic leukemia [18, 19]. Although serum β2-microglobulin is considered a reflection of tumor mass, we observed that there was a significantly positive correlation between age and serum β2-microglobulin levels. Thus, the prognostic significance of serum β2-microglobulin may be partially explained by this finding.

We conclude that advanced age and anemia appear to be the two dominant prognostic factors for survival after the initiation of treatment in patients with WM. When baseline serum β2-microglobulin levels are unavailable, these two readily available variables can stratify the patients into three distinct subgroups, and may help the selection of appropriate treatment and the evaluation of the effect of treatment.

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