*British Journal of Haematology*, 2001, **115**, 575–582

# Waldenström macroglobulinaemia: presenting features and outcome in a series with 217 cases

Ramón García-Sanz, Silvia Montoto, Agustín Torrequebrada, Alfonso García de Coca, José Petit, Anna Sureda, José Antonio Rodríguez-García, Pilar Massó, Ana Pérez-Aliaga, María Dolores Monteagudo, Isabel Navarro, Gemma Moreno, Carmen Toledo, Aránzazu Alonso, Carles Besses, Joan Besalduch, Isidro Jarque, Perla Salama, José Angel Hernández Rivas, Blanca Navarro, Joan Bladé and Jesús F. San Miguel *Spanish Group for the Study of Waldenström Macroglobulinaemia and PETHEMA (Programme for the Study and Treatment of Haematological Malignancies)*

*Received 9 May 2001, accepted 12 July 2001*

**Summary.** In this report we analyse the presenting features of a series of patients diagnosed with Waldenström macroglobulinaemia (WM) in Spain over the last 10 years. Criteria for diagnosis required a serum monoclonal IgM protein $\geq 30$ g/l and $> 20\%$ bone marrow lymphocytes. Two hundred and seventeen patients were included in the study, with a median age of 69 years and male/female ratio of 2:1. The most common symptoms at diagnosis were anaemia (38%), hyperviscosity (31%), B symptoms (23%), bleeding (23%) and neurological symptoms (22%). Sixty-one patients (27%) were asymptomatic at diagnosis and, to date, 32 of them have not received chemotherapy. Variables predicting a shorter survival free of therapy were haemoglobin $< 12{\cdot}5$ g/dl and high $\beta_2$microglobulin (β2M). The 83% of patients who did receive treatment were distributed as follows: chlorambucil/prednisone (43%), intermittent chlorambucil (11%), continuous chlorambucil (26%), cyclophosphamide/vincristine/prednisone (COP, 13·5%) and other (6·5%). Response to therapy was complete in 2%, partial in 48% and minor in 10%. Finally, 28% and 13% of patients presented stable and progressive disease, respectively, which was more common among patients treated with COP. Progression-free survival was 43% at 5 years, with three independent predictors for shorter progression-free survival (PFS): COP treatment, age $> 65$ and B symptoms at diagnosis. The 10-year projected overall survival (OS) was 55%. The two most frequent causes of death were development of second malignancies (31%), or infections (19%). The two main variables predicting a poor OS were hyperviscosity and high β2M. In summary, this study favours the use of chlorambucil-based therapy as the standard treatment for WM, and describes a subset of patients who should be considered as suffering a smouldering form and who therefore do not require treatment for a long period of time.

**Keywords:** Waldenström macroglobulinaemia, clinical picture, biology, prognosis, therapy.

Waldenström macroglobulinaemia (WM) is a monoclonal lymphoproliferative disorder characterized by the proliferation of neoplastic B cells infiltrating the bone marrow (BM) and other lymphoid organs with the capacity to synthesize and secrete high amounts of monoclonal immunoglobulin-M (IgM) (Waldenström, 1944, 1986; Brouet & Fermand, 1986; Dimopoulos & Alexanian, 1994). Clinical features include a more frequent presentation in men $> 50$ years old, the presence of hyperviscosity, organomegaly and cytopenias (Waldenström, 1986; Dimopoulos & Alexanian, 1994). Patients are usually treated with low doses of chlorambucil or combination chemotherapy (Case *et al*, 1991; Kyle, 1991; Dimopoulos *et al*, 1994) although new approaches with purine analogues such as fludarabine and 2-chlorodeoxyadenosine are increasingly used; (Dimopoulos *et al*, 1993, 1994; Dhodapkar *et al*, 2001).

Correspondence: Ramón García Sanz, Department of Haematology, University Hospital of Salamanca, Paseo de San Vicente, 58–182, Salamanca, 37007, Spain. E-mail: ramongarcia@aehh.org

WM is a rare disease, with an estimated incidence of only 6% of all B-cell lymphoproliferative disorders (Dimopoulos & Alexanian, 1994) implying a global incidence of two to five new cases per million persons per year (Herrinton & Weiss, 1993; Groves *et al*, 1998). Owing to this low prevalence, information on the disease is scanty, and most reported series are based on low numbers of patients. Moreover, the criteria to establish the diagnosis of WM are not homogeneous. In this regard, the minimum range of monoclonal IgM varies from 5 g/l (Dimopoulos & Alexanian, 1994;

Morel *et al*, 2000) 10 g/l (Gobbi *et al*, 1994; Andriko *et al*, 1997) or 30 g/l (Kyle & Garton, 1987). In addition, the minimum lymphocyte BM infiltration required is also variable: 30% (Gobbi *et al*, 1994), 25% (Facon *et al*, 1993) or just an 'increase' in the number of lymphocytes or plasmacytoid lymphocytes in the BM (Kyle & Garton, 1987). The availability of specific criteria for diagnosis of WM is very important in order to exclude other related disorders such as B-cell chronic lymphocytic leukaemia (CLL) or lymphomas with associated IgM monoclonal component or cases of IgM monoclonal gammopathy of uncertain significance. Moreover, unlike other B-cell malignancies, the information on prognostic factors is also limited (Waldenström, 1986; Facon *et al*, 1993; Dimopoulos & Alexanian, 1994; Gobbi *et al*, 1994; Morel *et al*, 2000) and there are no classifications based on stratification of patients into different risk categories in order to help individualize treatment.

Taking all these considerations into account, we have analysed the main clinical and biological characteristics of a large series of 217 WM patients diagnosed in Spanish institutions covering seven million inhabitants, over the last 10 years, according to the restrictive criteria of a minimum IgM monoclonal component of 30 g/l. In addition, the therapeutic protocols and the response to treatment are revised, including a detailed analysis of prognostic factors that could influence the disease outcome and the design of future therapeutic strategies.

## PATIENTS AND METHOD

*Patients.* Forms from 345 consecutive patients from 46 Spanish institutions diagnosed between December 1989 and December 1999 were submitted to the central secretary. All together, these institutions cover a population of around seven million inhabitants. One hundred and twenty-eight patients were excluded from the study because, although they had an IgM monoclonal paraprotein, they did not fulfil the WM diagnosis criteria required by the present study: (i) presence of a serum monoclonal IgM protein of at least 30 g/l at diagnosis; (ii) presence of bone marrow (BM) lymphocytosis ($> 20\%$) or $> 5\%$ lymphoplasmacytes. Finally, 217 patients fulfilled these criteria and constituted the basis for this study.

The database included the following parameters: age, sex, performance status [according to the Eastern Co-operative Oncology Group (ECOG) scale], presence of B symptoms or those associated with hyperviscosity syndrome, lymph node, spleen and liver enlargement, extranodal involvement, especially those yielding neurological, visual or renal deficiencies, percentage of lymphoid and lymphoplasmacytoid bone marrow infiltration, blood cell counts, monoclonal IgM, polyclonal IgG and IgA, serum albumin and $\beta_2$microglobulin ($\beta_2$M) levels, cryoglobulinaemia, cold agglutinins, Coombs test, Bence Jones proteinuria, type of light chain, serum level of lactate dehydrogenase (LDH), C-reactive protein (CRP) and myelin-associated antibodies. $\beta_2$M was available in only 133 cases and its absolute values were corrected according to the normal ranges provided by each laboratory, and the value that was introduced into the database was the ratio between the obtained value/upper normal values. CRP was excluded in the multivariate analyses because it was available in only 65 patients. Data on treatment included the chemotherapeutic regimen, response to therapy and time to progression after treatment.

The response to therapy was evaluated at 6 or 12 months from initiation. Partial response (PR) was defined as a reduction of 50% or more of the monoclonal component, with more than a 50% reduction of bone marrow lymphocytosis and lymph node enlargement or organomegaly if present. Responding patients should be free of symptoms, and the blood counts should be within normal limits. Complete response (CR) was defined as the disappearance of the monoclonal protein by immunofixation (both in serum and urine), including the complete resolution of lymphadenopathy and organomegaly, and $< 20\%$ lymphocytes and $< 5\%$ lymphoplasmacytes in the bone marrow. Those patients who fulfilled all the above criteria but $< 50\%$ reduction of M-component were considered to have a minimal response (MR). When the criteria for a PR or MR were not fulfilled, the case was considered a treatment failure. Finally, a distinction between no change (NC) and progressive disease (PD) was also made.

Progression was defined as an increase of $> 50\%$ from the lowest level of serum M-component achieved with the initial therapy; an increase in size or number of enlarged lymph nodes or organomegaly, or in the bone marrow infiltration by lymphocytes or lymphoplasmacytes and the development of new extranodal involvement or cytopenias.

Overall survival (OS) was considered from the time of diagnosis to death, and progression-free survival (PFS) from diagnosis to the moment at which the progression was noted. In addition, we have evaluated the survival free of treatment (SFT), considered as the time elapsed between the diagnosis and the moment at which the therapy had to be started because of the presence of signs or symptoms of disease activity. Duration of response was considered as the time between the moment at which the maximum response was achieved and the moment of progression.

*Therapeutic protocols.* The protocols used for the treatment of the patients analysed here included mainly chlorambucil-based regimens (80%), although other regimens were also used. The majority of patients (43%) received chlorambucil combined with prednisone according to the Spanish PETHEMA (Programme for the Study and Treatment of Haematological Malignancies) CLL protocol (Spanish Cooperative Group on CLL, 1991), which included oral prednisone (60 mg/m$^2$/d) on d 1–4 and oral chlorambucil (0·4 mg/kg body weight/d) on d 5 and d 6, repeated every 2 weeks. The treatment was intended to be maintained for a minimum of 6 months and a maximum of 12 months. In 11% of patients, chlorambucil was used alone but with the same schedule, whereas the remaining 26% of patients received continuous chlorambucil (2–5 mg/d depending on the tolerance). The COP regimen was used in 13·5% of cases and included the use of intravenous cyclophosphamide (750 mg/m$^2$) and vincristine (2 mg) on d 1 with oral prednisone (60 mg/m$^2$/d) on d 1–5. The COP protocol was

administered every 3–4 weeks for a minimum of six cycles. Five per cent of patients received melphalan and prednisone according to the PETHEMA Spanish protocol used for multiple myeloma patients (Bladé *et al*, 1993), which includes the use of oral melphalan (9 mg/m$^2$/d) and oral prednisone (60 mg/m$^2$/d) for 4 d. This treatment was administered every 4 weeks for a minimum of 12 months. Finally, only 1·5% of patients were treated with purine analogues (fludarabine and 2-chloro-deoxyadenosine) according to standard protocols.

Criteria to start therapy included the presence of clinical symptoms or cytopenias secondary to the disease at the moment of diagnosis, or the presence of evidence of progressive disease (e.g. anaemia, lymph node enlargement or increase in M-component size). In all cases, once treatment was started, the minimum duration was 6 months. Plasmapheresis was also indicated in the presence of symptoms or signs of hyperviscosity syndrome. With these criteria, plasmapheresis was carried out in 16% of cases, with a median of three aphereses per case (range 1–57), including two patients that were treated with this therapeutic modality alone. Finally, other therapeutic measures (transfusions, adjuvant steroid for haemolytic anaemia, analgesics, etc.) were taken if necessary.

*Statistical method.* All analyses were performed with the Statistical Package software for Social Sciences (SPSS 9·0; SPSS Inc Chicago, IL, USA). All characteristics mentioned above were correlated individually with probability of CR, PR or MR and the rate of progression for these responses according to univariate tests (*t*-test, chi square test, correlations and non-parametric tests, SPSS). Subsequently, a multivariate analysis –stepwise regression– (regression, SPSS) (Norusis, 1990; Reeves *et al*, 1998) was performed to examine the simultaneous effect of the different variables on the probability of achieving CR and the rate of relapse.

The same characteristics were subsequently considered for analysis concerning their individual and simultaneous effects on SFT, OS, and PFS. OS and PFS curves were plotted using the method of Kaplan & Meier (1958). Statistical comparisons between actuarial survival curves were based on log rank, Peto Prentice and Breslow tests. The cut-off point of each variable was selected by starting at its median value and then cutting at different levels above and below, until significance was obtained. Variables considered for possible inclusion in the regression analysis were those for which there was some indication of a significant association in univariate analysis ($P < 0{\cdot}1$) or for which previous studies had suggested a possible association. The stepwise regression procedure was stopped when the *P*-value for entering an additional factor was $>0{\cdot}05$. The model was tested both by expressing values in a continuous way (continuous variables) and by grouping them into categories (dichotomous variables).

## RESULTS

### *Clinical and biological characteristics at diagnosis*

Overall, two hundred and seventeen patients fulfilled the diagnostic criteria and were included in the study. All cases fitted the disease criteria already at the moment of diagnosis, with the exception of eight patients who reached the level of 30 g/l during the immediate follow-up (< 3 months). The median age at diagnosis was 69 years and the male/female ratio was 2:1. Twenty-seven per cent of patients were asymptomatic at presentation. The most common relevant symptoms in the remaining patients were anaemia (38%), hyperviscosity-related symptoms (31%), B symptoms (23%), bleeding (23%) and neurological symptoms (22%). There were eye fundic changes in 34% of cases, whereas lymphadenopathy, hepatomegaly and splenomegaly were present in 25%, 24% and 19% respectively. The median monoclonal IgM was 44 g/l (range 30–13·4) and the presence of light chains in urine was found in 31% of patients. Absolute lymphocytosis ($\geqslant 5{\cdot}10^9$/l) was present in 9% of cases, and the LDH was high in 11% of them. In contrast, $\beta_2$M was above the maximum normal limit in 54% (median 1·1-times the normal value, range 0·1–5·1). Thrombocytopenia ($\leqslant 50 \times 10^9$/l) and neutropenia ($\leqslant 1{\cdot}0 \times 10^9$/l) were observed in 2·4% and 4·3% of patients respectively. The Coombs test was positive in 10% of patients but only 3% developed significant haemolysis. No osteolytic lesions were observed, but severe osteoporosis was noted in 7% of patients. Finally, involvement of other organs was rare: lung (4%), kidney (4%), gut (3%) and skin (3%). Cold agglutinins were positive in 5% of cases, although only 1·5% of patients had symptomatic cold agglutinin syndrome.

### *Time to therapy*

At presentation, 61 patients were asymptomatic, whereas at the time of this analysis only 32 patients (14·7%) had not received any chemotherapy because they remained asymptomatic with no evidence of disease progression. In addition, four symptomatic patients (1·8%) did not receive chemotherapy because of patient refusal (two cases) and severe septicaemia resulting in death (two cases). This implies that within the asymptomatic patients the projected SFT showed a continuous descending curve, with the estimated proportion of patients free of therapy as only 13% after 10 years of diagnosis (Fig 1).

Within asymptomatic patients, the analysis of prognostic

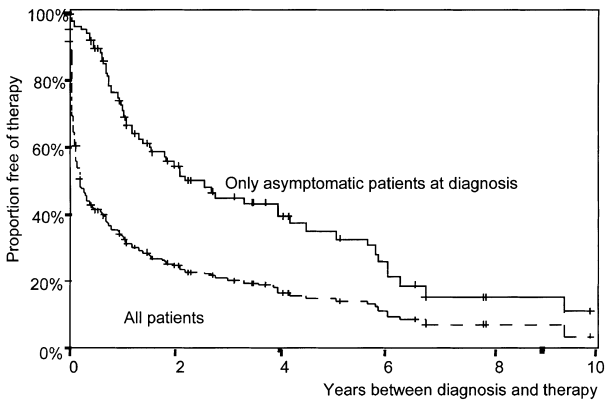


**Fig 1.** Survival free of therapy in WM.

factors showed that the variables predicting a shorter time free of therapy were the presence of a haemoglobin level $< 12{\cdot}5$ g/dl ($P < 0{\cdot}0001$), a high serum $\beta_2$M ($P = 0{\cdot}03$) or a monoclonal IgM $\geqslant 40$ g/l ($P = 0{\cdot}01$). In multivariate analysis, only the first two variables retained an independent prognostic significance. The age, sex, LDH serum level, antiglobulin test, splenomegaly, hepatomegaly, decrease of normal immunoglobulins (low IgG or IgA), white blood cell (WBC) count and lymphocyte count did not have any influence on the future need for treatment.

*Response to front line therapy*

Eighty-three percent of patients have already received treatment with chemotherapy. Most of them (68%) received the therapy within the first 3 months after diagnosis because of the presence of symptomatic disease. The remaining cases were asymptomatic at diagnosis and received the treatment more than 3 months after diagnosis because they finally developed clinical symptoms (52% of cases) or because they demonstrated a sustained elevation of the monoclonal IgM peak without symptomatic disease (48% of cases).

Table I shows the response to the different regimens used. Complete responses were achieved in only 2% of cases. Forty-eight percent of patients achieved a PR and 10% a MR. Finally, 28% of cases showed no changes after first-line therapy, whereas in 13% the disease showed a progressive pattern. As shown in Table I, the worst results were obtained with the COP regimen as up to 22% of cases progressed under this therapy, whereas this percentage was only 13% in the patients treated with the other regimens. However, these differences did not reach statistical significance, although the sum of patients with progressive or stable disease was 49% in the group of patients treated with COP, and 28% in patients treated with chlorambucil-based protocols ($P = 0{\cdot}043$). Both groups, those treated with COP and those treated with other regimens, were compared for several prognostic factors and no significant differences between them were found.

The analysis of factors predicting the response showed that progressive disease was associated with the presence of neuropathy ($P = 0{\cdot}02$), hyperviscosity symptoms ($P = 0{\cdot}04$), Hb level $< 11{\cdot}5$ g/dl ($P = 0{\cdot}04$) or IgA serum level $< 1$ g/l ($P = 0{\cdot}05$). Discriminant analysis showed that the two factors independently associated with a progressive disease after treatment were neuropathy ($P = 0{\cdot}018$) and anaemia ($P = 0{\cdot}03$). Interestingly, the presence of a normal $\beta_2$M level was associated with a stable disease ($P = 0{\cdot}026$). However, the age, M-component, WBC and granulocyte count, serum level of IgG, C-reactive protein or LDH and proportion of bone marrow-infiltrating cells did not relate to the quality of response. Duration of response was dependent on age (shorter in patients $> 65$ years), the presence of B symptoms (shorter if present) and LDH serum level (shorter if higher than the normal maximum limit).

*Outcome*

Forty-eight percent of patients receiving treatment have already progressed, which results in a projected PFS of only 43% and 28% at 5 and 10 years respectively (median, 46 months). The COP chemotherapy resulted in a shorter PFS than the remaining regimes (22 versus 53 months, $P < 0{\cdot}0001$). Other variables that also predicted a shorter PFS were age $< 65$ years, presence of symptomatic disease at diagnosis, Hb $< 12{\cdot}5$ g/dl, IgM $> 50$ g/l, hyperviscosity syndrome, hepatomegaly, and fundic changes (Table II). In the multivariate analysis, three variables were selected as independent predictors for shorter PFS: COP treatment ($P = 0{\cdot}0002$), age greater than 65 ($P = 0{\cdot}003$) (Fig 2) and presence of B symptoms at diagnosis ($P = 0{\cdot}018$).

Concerning overall survival (OS), 52 patients (24%) had died at time of evaluation, resulting in a projected overall survival of 55% at 10 years. The most frequent cause of death was the development of second malignancies, which was responsible for 16 deaths (31%). The most frequent associated neoplasms were: lung cancer ($n = 4$, 7·7%), myelodysplastic syndrome ($n = 3$, 5·8%) and colon cancer ($n = 3$, 5·8%). Three cases evolved into an aggressive non-Hodgkin's lymphoma (5·8%) while three other patients

**Table I.** Response to the therapy.

| | | Response | | | | |
|---|---|---|---|---|---|---|
| Therapy | *n* | Complete (%) | Partial (%) | Minimal (%) | Stable disease (%) | Progression (%) |
| None | 36 | 0 | 0 | 0 | 89 | 11 |
| Chlorambucil and prednisone | 79 | 4 | 56 | 10 | 14 | 16 |
| Intermittent chlorambucil | 20 | 0 | 75 | 15 | 10 | 0 |
| Continuous chlorambucil | 46 | 2 | 52 | 15 | 17 | 13 |
| COP | 22 | 0 | 41 | 10 | 27 | 22 |
| Melphalan and prednisone | 8 | 0 | 75 | 0 | 25 | 0 |
| Other | 6 | 0 | 50 | 17 | 33 | 0 |
| Total* | 217 | 2 | 46 | 10 | 28 | 18 |

*Patients not receiving chemotherapy were excluded for global calculations.
Overall, the differences were not statistically different (chi-square test, $P > 0{\cdot}05$).

**Table II.** Univariate and multivariate analysis of prognostic factors for OS and PFS.

| | Progression-free survival ($n = 181$) | | | | Overall survival ($n = 217$) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | Median | P Univariate | P Multivariate | *n* | Median | P Univariate | P Multivariate | |
| Variable | | | | | | | | Without β2M | With β2M |
| Symptoms at diagnosis | | | | | | | | | |
| No | 56 | 77 | 0·0017 | 0·0179 | 88 | 209 | 0·0000 | 0·0016 | – |
| Yes | 125 | 40 | | | 129 | 84 | | | |
| Age | | | | | | | | | |
| ≤ 65 years | 72 | 31 | 0·0001 | 0·0003 | 82 | 209 | 0·0431 | 0·0024 | – |
| > 65 years | 109 | 77 | | | 135 | 80 | | | |
| Haemoglobin | | | | | | | | | |
| ≤ 10·5 g/dl | 91 | 40 | 0·3268 | – | 97 | 84 | 0·0025 | 0·0193 | – |
| > 10·5 g/dl | 89 | 58 | | | 120 | 209 | | | |
| Hyperviscosity | | | | | | | | | |
| No | 64 | 58 | 0·0021 | – | 150 | 209 | 0·0001 | – | 0·0068 |
| Yes | 117 | 28 | | | 67 | 58 | | | |
| β2microglobulin | | | | | | | | | |
| Low | 47 | 58 | 0·6010 | – | 66 | NR | 0·0172 | – | 0·0254 |
| High | 68 | 45 | | | 77 | 84 | | | |
| Treatment | | | | | | | | | |
| No | 36 | – | – | – | 36 | NR | | | |
| COP | 22 | 22 | 0·0000 | 0·0002 | 22 | 58 | 0·1021 | – | – |
| Other | 159 | 53 | | | 137 | 141 | | | |
| Urine M-comp | | | | | | | | | |
| No | 60 | 43 | 0·6351 | – | 150 | NR | 0·0397 | – | – |
| Yes | 121 | 53 | | | 67 | 80 | | | |
| Hepatomegaly | | | | | | | | | |
| No | 134 | 53 | 0·0315 | – | 164 | 209 | 0·0459 | – | – |
| Yes | 47 | 25 | | | 53 | 88 | | | |
| M-component | | | | | | | | | |
| ≤ 45 g/l | 53 | 91 | 0·0984 | – | 117 | 209 | 0·0292 | – | – |
| > 45 g/l | 41 | 90 | | | 0100 | 84 | | | |

developed pancreatic and gastric carcinomas, as well as a metastastic cancer of unknown primary site. The frequency of second malignancies was similar between patients treated with chemotherapy (7·8%) and those who did not receive it (5·3%). The second cause of death was infection (19%), mainly septicaemia ($n = 7$) and pneumonia ($n = 3$). Progressive disease was considered as the cause of death in 5 cases (9·6%), while the remaining causes were: congestive heart failure ($n = 5$, 9·6%), cerebral haemorrhage ($n = 4$, 7·7%), renal insufficiency ($n = 4$, 7·7%), hepatic failure ($n = 1$, 1·9%) and hypercalcaemia ($n = 1$, 1·9%). Finally, there were six deaths (11·5%) presumably not related to WM: end-stage diabetes ($n = 2$), intracranial thrombosis ($n = 1$), polyarteritis nodosa ($n = 1$), obstructive lung disease ($n = 1$) and anaphylaxis ($n = 1$).

The univariate analysis showed that the following factors were associated with a poor OS: symptomatic disease at diagnosis ($P = 0·0001$), hyperviscosity syndrome ($P = 0·0001$), haemoglobin $< 11·5$ g/dl ($P = 0·0018$), high $\beta_2 M$ ($P = 0·0175$), urinary excretion of monoclonal light chains ($P = 0·0397$), IgM > 45 g/l ($P = 0·0292$), age > 65 years ($P = 0·0103$) and the presence of liver enlargement at diagnosis ($P = 0·0459$). In the multivariate analysis, the three variables with independent prognostic value were the presence of symptomatic disease at diagnosis ($P = 0·0016$), age older than 65 ($P = 0·0024$) and Hb $< 11·5$ g/dl (0·0193). In this analysis, β2M was first excluded because it was only available in 66% of cases. When the β2M was also included (available cases, $n = 143$) the two variables selected were hyperviscosity symptoms and high β2M.

## DISCUSSION

In this report we have analysed a large series of WM patients diagnosed according to restrictive criteria, such as the presence of a minimum IgM monoclonal component of 30 g/l. Over 10 years, 217 patients fitted these diagnostic criteria. According to our calculations, this yield an estimated incidence of 4·2 cases per million person-years

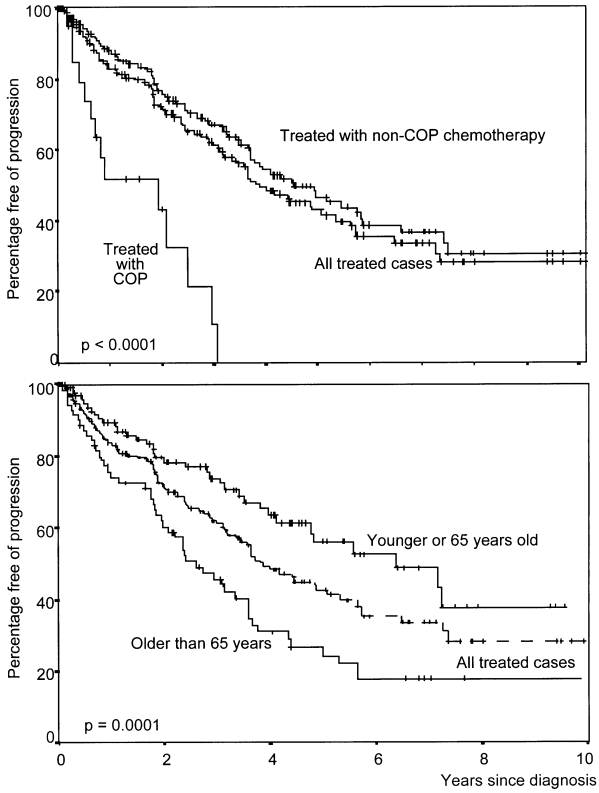


**Fig 2.** Progression-free survival of WM patients and main prognostic factors.

at risk among men and 2·0 per million among women. This incidence is similar to those reported in the USA, where the annual incidence ranges between 3·4 and 6·1 per million in white men and between 1·7 and 2·5 in white women (Herrinton & Weiss, 1993; Groves *et al*, 1998), although some bias could vary the estimation made in this paper.

The clinical and biological features that our patients exhibited are not very different from those already reported (reviewed by Dimopoulos *et al*, 2000). The most remarkable difference was the existence of a slightly higher frequency of symptoms in our series, especially those objective signs indicating active disease (liver, spleen and lymph node enlargement, bleeding and neurological manifestations). This difference might be caused by the diagnostic criteria used here because it is well known that the symptoms are usually more frequent in patients with high M-component ($> 30$ g/l). The findings related to the time to therapy are of particular interest. Our observations indicate that most WM patients fulfilling the criteria used here will require chemotherapy at some time. Interestingly, only those patients with a completely normal haemoglobin level ($\geqslant 12{\cdot}5$ g/dl) and normal β2M serum level will probably be free of therapy for a long time. This may represent a very useful diagnostic tool to identify which patients will probably not require therapy in the future and could be considered to be smouldering WM.

As far as the chemotherapeutic treatment is concerned, it is interesting to note that chlorambucil-based regimens can achieve better and longer responses than a COP regimen. This is not a randomized study, so these findings must be interpreted with caution. However, the fact that no important differences were found between patients treated with one protocol or another and the fact that the COP regimen was selected as an adverse prognostic factor for the PFS favours the hypothesis that this is not an appropriate regimen for WM. Other studies have also shown good results with chlorambucil for WM patients (Kyle *et al*, 2000), and there is no data in the literature supporting the superiority of other regimens on long-term follow-up (reviewed by Dimopoulos *et al*, 2000). Because very few patients received purine analogues in our study we cannot reach any conclusions, but it will be of interest for future studies to compare strategies containing these drugs with those including chlorambucil.

The analysis of prognostic factors confirms that patients with more advanced disease at presentation (with symptomatic disease or anaemia) and those with advanced age had a shorter survival. This is also consistent with the fact that the most frequent causes of death were complications related to the disease, such as infections and second malignancies (reviewed by Dimopoulos *et al*, 2000). The latter aspect could be associated with the advanced age of patients with WM. Nevertheless, the observed incidence of second neoplasias is higher than that expected in the general population, which would suggest that the risk of second malignancies is increased in WM, probably because of the combination of several factors such as advanced age, long-term alkylating therapy and immunosurveillance defects (García *et al*, 1993). Based on this data, the appearance of second malignancies in a WM patient should no longer be considered as an event unrelated to the underlying disease.

The present analysis could yield two score prognostic systems to predict PFS and OS that can be prospectively tested in another populations. However, this will not be possible for the scoring system concerning the PFS because the COP therapy will not be used any more as a first-line therapy in our protocols. In contrast, the scoring system for OS (β2M level and the presence of hyperviscosity symptoms) will be tested in the next therapeutic protocol that the PETHEMA group will initiate for WM.

In summary, this study supports the use of chlorambucil-based therapy as the standard treatment for WM compared with COP-like regimens. In addition, it shows that the presence of hyperviscosity symptoms and elevated $\beta_2$M confer a poor prognosis on the disease. Finally, we have identified a cohort of patients that should be considered as smouldering WM who do not require treatment for a long period of time.

## CONTRIBUTIONS AND ACKNOWLEDGMENTS

R.G.-S. designed the study, collected the data, performed the analysis and wrote the paper in its initial version. J.B. and J.F.S.M. were chiefly responsible for the group, stimulated the work, supported the collection of data and contributed to the writing of the paper and gave final approval for the version to be submitted.

The remaining authors present in the list were the clinicians responsible for the patients and the data collection in each individual institution. Those responsible, institutions and numbers of patients (in brackets) included in the paper were as follows: R.G.-S., Hospital Universitario de Salamanca (19); S.M., Hospital Clinic i Provincial de Barcelona (16); A.T., Hospitals Vall D'Hebron de Barcelona (14); A.G.dC., Hospital Universitario de Valladolid (10); J.P., Institut Catalá D'Oncología (10); A.S., Fundació de GS de L'Hospital de la Santa Creu i Sant Pau de Barcelona (9); J.A.R.-G., Hospital del Bierzo de Ponferrada (8); P.M., Hospital Ramón y Cajal de Madrid (8); A.P.-A., Hospital Universitario Doctor Peset (8); M.D.M., Complejo Hospitalario Móstoles/Alcorcón (7); I.N., Hospital Francesc de Borja de Gandia (7); G.M., Hospital Severo Ochoa de Leganés (5); C.T., Complejo Hospitalario La Salud de Toledo (5); A.A., Hospital de La Princesa de Madrid (5); C.B., Hospital del Mar de Barcelona (4); J.B., Complejo Asistencial Son Dureta de Palma de Mallorca; I.J., Hospital Universitario La Fe de Valencia (4); P.S., Hospital Doce de Octubre de Madrid (4); J.A.H.-R., Consorci Sanitari de Mataró (4); J.B., Hospital Clinic i Provincial de Barcelona; J.F.S.M., Hospital Universitario de Salamanca.

In addition, the following clinicians and Hospitals contributed three patients: Antonio Asensio from the Hospital Residencia de Sant Camil de Sant Pere de Ribes, Carmen Martínez from the Clínica Ruber S.A., Eduardo Ríos from the Hospital Universitario Virgen del Rocío de Sevilla, Jerónima Ibáñez from the Hospital General de Área Santa María del Rosell de Cartagena, L. Javier García-Frade from the Hospital del Rio Hortega de Valladolid, Luis Palomera from the Hospital Clínico Universitario Lozano Blesa de Zaragoza and Santiago Gardella from the Hospital de Girona Josep Trueta. The following clinicians and centres included contributed two patients: Alfons Soler from the Consorci Hospitalari del Parc Taulí, Antonio Montero from the Hospital Universitario del Aire, Elena Pérez from the Hospital General Universitario de Murcia, Elena Revilla from the Hospital Comarcal de L'Alt Penedès, Fernando Solano from the Hospital NS del Prado de Talavera, Germán Las Heras from the Hospital de Martorell, González Hurtado from the Hospital Virgen del Puerto de Plasencia, M[a] Jesús Arilla from the Hospital de Sagunto and M[a] Guniot Martínez from the Hospital General de Castellón. Finally, the following clinicians and centres contributed one patient: Esperanza Tuset from the Hospital General de Manresa, Isabel Cano from the Complejo Hospitalario La Mancha Centro de Alcázar de San Juan, José M[a] Fernández-Rañada from the Clínica la Moncloa de Madrid, M[a] José Calmuntia from the Hospital General de Segovia and M[a] José Otero from the Hospital Gómez Ulla.

This work has been possible thanks to Mark Anderson's technical assistance, the facilities of the Public Spanish National Health System and the collaboration of Janssen-Cilag España, who provided close contact through Blanca Navarro and who is now the clinician of three patients included in the series.

## REFERENCES

Andriko, J.-A., Aguilera, N.S.I., Chu, W.S., Nandedkar, M.A. & Cotelingam, J.D. (1997) Waldenström's macroglobulinemia. A clinicopathologic study of 22 cases. *Cancer*, **80**, 1926–1935.

Bladé, J., San Miguel, J.F., Alcalá, A., Maldonado, J., Sanz, M.A., García-Conde, J., Moro, M.J., Alonso, C., Besalduch, J., Zubizarreta, A., Besses, C., González Brito, G., Hernández-Martín, J., Fernández-Calvo, J., Rubio, D., Ortega, F., Jiménez, R., Colominas, P., Faura, M.V., Font, L., Tortosa, J., Domingo, A., Fontanillas, M., Rozman, C. & Estapé, C. (1993) Alternating combination VCMP/VBAP chemotherapy versus melphalan/prednisone in the treatment of multiple myeloma: a randomized multicentric study of 487 patients. *Journal of Clinical Oncology*, **11**, 1165–1171.

Brouet, J.C. & Fermand, J.P. (1986) Macroglobulinémie de Waldenström. *Hemopathies Malignes* (ed. by R. Zittoun), pp. 539–553. Flammarion, Paris.

Case, D.R., Ervin, T.J., Boyd, M.A. & Redfield, D.L. (1991) Waldenström macroglobulinemia: long term results with the M2 protocol. *Cancer Investigation*, **9**, 1–7.

Dhodapkar, M.V., Jacobson, J.L., Gertz, M.A., Rivkin, S.E., Roodman, G.D., Tuscano, J.M., Shurafa, M., Kyle, R.A., Crowley, J.J. & Barlogie, B. (2001) Prognostic factors and response to fludarabine therapy in patients with Waldenstrom macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood*, **98**, 41–48.

Dimopoulos, M.A. & Alexanian, R. (1994) Waldenström macroglobulinemia. *Blood*, **83**, 1452–1459.

Dimopoulos, M.A., Kantarjian, H., Estey, E., O'Brien, S., Delasalle, K., Keating, M.J., Freireich, E.J. & Alexanian, R. (1993) Treatment of Waldenström macroglobulinemia with 2-chlorodeoxyadenosine. *Annals of Internal Medicine*, **118**, 195–198.

Dimopoulos, M.A., Kantarjian, H., Weber, D., O'Brien, S., Estey, E., Delasalle, K., Rose, E., Cabanillas, F., Keating, M. & Alexanian, R. (1994) Primary therapy of Waldenström macroglobulinemia with 2-chlorodeoxyadenosine. *Journal of Clinical Oncology*, **12**, 2694–2698.

Dimopoulos, M.A., Panayiotidis, P., Moulopoulos, L.A., Sfikakis, P. & Dalakas, M. (2000) Waldenstrom's macroglobulinemia: clinical features, complications, and management. *Journal of Clinical Oncology*, **18**, 214–226.

Facon, T., Brouillard, M., Duhamel, A., Morel, P., Simon, M., Jouet, J.P., Bauters, F. & Fenaux, P. (1993) Prognostic factors in Waldenström macroglobulinemia: a report of 167 cases. *Journal of Clinical Oncology*, **11**, 1553–1558.

García, R., Hernandez, J.M., Caballero, M.D., Gonzalez, M. & San Miguel, J.F. (1993) Immunoblastic lymphoma and associated non-lymphoid malignancies following two cases of Waldenström's macroglobulinemia. A review of the literature. *European Journal of Haematology*, **50**, 299–301.

Gobbi, P.G., Bettini, R., Montecucco, C., Cavanna, L., Morandi, S., Pieresca, C., Merlini, G., Bertoloni, D., Grignani, G. & Pozzetti, U. (1994) Study of prognosis in Waldenström's macroglobulinemia. a proposal for a simple binary classification with clinical and investigational utility. *Blood*, **83**, 2939–2945.

Groves, F.D., Travis, L.B., Devesa, S.S., Ries, L.A.G. & Fraumeni, J.F. (1998) Waldenström's macroglobulinemia. Incidence patterns in the United States, 1988–94. *Cancer*, **82**, 1078–1081.

Herrinton, L.J. & Weiss, N.S. (1993) Incidence of Waldenström's macroglobulinemia. *Blood*, **10**, 3148–3150.

Kaplan, E. & Meier, P. (1958) Nonparametric estimation from incomplete observations. *Journal of the American Statistics Association*, **53**, 457–464.

Kyle, R.A. & Garton, J.P. (1987) The spectrum of IgM monoclonal gammopathy in 430 cases. *Mayo Clinic Proceedings*, **62**, 719–731.

Kyle, R.A., Greipp, P.R., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q. & Therneau, T.M. (2000) Waldenström's macroglobulinaemia.

a prospective study comparing daily with intermittent oral chlorambucil. *British Journal of Haematology*, **108**, 737–742.

Kyle, R.A. (1991) Plasma cell proliferative disorders. In: *Hematology Basic Principles and Practice* (ed. by R. Hoffman, E.J. Benz, S.J. Shattil, B. Farie & H.J. Cohen), pp. 1021–1029. Churchill Livingstone, New York.

Morel, P., Monconduit, M., Jacomy, D., Lenain, P., Grosbois, B., Bateli, C., Facon, T., Dervite, I., Bauters, F., Najman, A., Gramont, A. & Wattel, E. (2000) Prognostic factors in Waldenström macroglobulinemia. a report on 232 patients with the description of a new scoring system and its validation on 253 other patients. *Blood*, **96**, 852–858.

Norusis, M.J. (1990) *SPSS® Base System User's Guide SPSS® 40 for the Macintosh*. SPSS Inc, Chicago, IL.

Reeves, G.K., Cox, D.R., Darby, S.C. & Whitley, E. (1998) Some aspects of measurement error in explanatory variables for continuous and binary regression models. *Statistics in Medicine*, **17**, 2157–2177.

Spanish Cooperative Group on CLL (1991) Treatment of chronic lymphocytic leukaemia: a preliminary report of Spanish (PETHEMA) trials. *Leukemia and Lymphoma*, **5**, 89–91.

Waldenström, J. (1944) Incipient Myelomatosis or 'essential' hyperglobulinemia with fibrinogenopenia. A New Syndrome? *Acta Medica Scandinavica*, **117**, 216–247.

Waldenström, J.G. (1986) Macroglobulinemia. A review. *Haematologica*, **71**, 437–440.