Prognostic evaluation of Waldenström's macroglobulinemia (WM) is unreliable, few studies considered prognostic factors in WM and only one was derived from a multivariate analysis. One hundred forty-four retrospective, previously untreated patients with clinically overt WM were studied to learn whether overall survival was related to any of the various clinical features presented at diagnosis. Patients were homogeneously treated with intermittent doses of chlorambucil for as long as this showed an effect on the monoclonal component. The population was randomly subdivided into a 90-patient exploratory sample, on whom investigation would be conducted, and in a 54-patient test sample, on whom the results would be validated. In the exploratory sample univariate analysis identified the following parameters as the most important for prognosis: age (< or ≥70 years), platelet count (< or ≥120 x 10^9/L), presence or absence of an abnormal number of red blood cells in the urine, hemoglobin concentration (< or ≥9 g/dL), erythrocyte sedimentation rate (< or ≥110 mm at first hour), presence or absence of cryoglobulinemia and of weight loss. Cox multivariate analysis showed that only hemoglobin, age, weight loss, and cryoglobulinemia independently affected survival. These four clinical variables were also shown to be able to discriminate survival significantly in the test sample. Moreover, it was possible to demonstrate (both in the exploratory and the test sample) that clear-cut, albeit dichotomic, survival discrimination can be reached with the presence at diagnosis of either no more than one, or any two or more, of these four prognosticators. These simple clinical criteria could be the basis of an initial binary, prognostic classification of WM, which could help in differentiating therapy according to the severity of the disease, and in properly designing future clinical trials.

WALDENSTRÖM’S macroglobulinemia (WM) is generally considered to correspond to a wide spectrum of closely related lymphoproliferative diseases that present, as a diagnostic hallmark, clonal proliferation of B lymphocytes or lymphoplasmacytic cells in bone marrow and/or in lymph nodes, and monoclonal immunoglobulin M (IgM) in the plasma.1

The literature on WM reflects a considerable interest regarding the variability of clinical picture, due to the large series of complications and damage determined by the physico-chemical properties or antibody activities of the monoclonal IgM.2-4 So, great attention has been given to the problems arising in correctly diagnosing and clinically monitoring some particular presentations,5-6 to the necessary therapeutic measures and to the most suitable timing for therapy.7 However, there is no clearly defined distinction between WM itself and its benign counterpart (ie, the so-called IgM monoclonal gammopathy of unknown significance, IgM-MGUS), or between a hypothetical “indolent” WM—if this term is nosologically justified—which does not require therapy, and an “overt” or “active” WM that must be treated.1,2,6-8 Moreover, few studies on WM are available,9,12 so treatment criteria based on actual patient needs have not yet been codified. The relative rarity of WM represents a major obstacle to the achievements of this goal.

Here we report the results of a retrospective prognostic study, performed on patients with clinically overt and homogeneously treated WM.

MATERIALS AND METHODS

Patient population. The population of the study consisted of 144 patients diagnosed and treated between 1976 and 1991 in four institutions in Northern Italy who fulfilled the following inclusion criteria: 1) previously untreated; 2) bone marrow B-lymphoid cell infiltration higher than 30% of total nucleated marrow cells; 3) presence of serum IgM monoclonal component of at least 10 g/dL; 4) start of therapy within 6 months since diagnosis (requirement of therapy due to signs or symptoms of disease is considered the most important discriminant from overt WM and MGUS1,7).

All patients were evaluated through clinical history, physical examination, and a laboratory investigation that included complete blood count, erythrocyte sedimentation rate at first hour, biochemical tests of liver and renal function, lactate dehydrogenase, serum and urinary protein dosage with protein electrophoresis and immunoelectrophoresis, bone marrow biopsy and aspiration, standard chest X-ray, liver and spleen ultrasonography, and skeletal X-ray when bone pain was present.

For the purposes of the study, the term “hemataria” included both the microscopic and the macroscopic presence of an abnormal amount of red blood cells in the urine. Hemorrhagic symptoms comprised visible bleeding, hematorax, ecchymotic and purpuric manifestations. Liver enlargement was evaluated by physical examination and confirmed with imaging techniques (abdominal ultrasonography and, in some cases, computed tomography). The parameter “weight loss” was irrespective of severity or rate: it corresponded to a minimum loss of 3 kg during the last 6 months.

Marrow infiltration was quantitatively measured using routinely processed core biopsies; histologic subtype evaluation (lymphoplasmacytic, lymphoplasmacytoid, polymorphous) was preferred to growth pattern recognition (nodular, interstitial, packed marrow),9 due to the easier reproducibility of the former among pathologists and the good interrelationship of both.9

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No IgM serum level, however high, was considered sufficient per se for a diagnosis of overt WM, whereas the definite presence of monoclonal serum IgM of at least 10 g/L, as demonstrated by standard electrophoretic and immuno-electrophoretic techniques, was necessary for diagnosis. This series also included 16 patients in whom the IgM monoclonal component was diagnosed by chance and a watchful-waiting management policy was first adopted in light of the mildness of their symptoms; however, they all became clearly symptomatic and required treatment within the following 6 months. In these cases the survival time was calculated from the onset of symptoms rather than from discovery of the monoclonal component.

Patient clinical and serologic characteristics are reported in Table 1. Treatment consisted of single alkylating agent chemotherapy with chlorambucil intermittently administered at a 0.1 to 0.2 mg/kg/d, 7 to 14 days per month, according to hematologic toxicity. In 28 patients therapy with prednisone was associated with chlorambucil in varying doses and schedules, generally 0.3 to 0.7 mg/kg/d, as long as the alkylating drug was administered; it was then quickly tapered at the beginning of the treatment interval. Steroid therapy was decided in the presence of hyperhemolysis, heavy bone marrow lymphoid infiltration, purpura, bone pain, and severe anemia.

When a good clinical response (stable or decreasing IgM electrophoretic peak) was achieved, the single-drug therapy was either continued with two- or threefold longer intervals or stopped for a variable length of time, until the monoclonal component rose once again. In the event of no response to initial treatment or of relapse, multiple drug chemotherapy was administered: CVB (cyclophosphamide, vincristine, prednisone in 6 to 9 cycles), or CHOP (the same drugs plus Adriamycin) were used most frequently. Plasmapheresis was used in 11 patients: three at onset, and at variable times in the course of the disease in the remaining eight.

**Statistics.** The population of the study was randomly subdivided into two casual and independent subsets of patients in about a 3:2 ratio. In the first group, the exploratory sample of 90 patients, we looked for clinical factors that demonstrated an important effect on prognosis. In the second, the test sample consisting of the remaining 54 patients, we evaluated the choice of prognostic factors. Clear differences in survival in relation to each of the four remaining factors, which therefore can be discarded.

The validation of these results is demonstrated in Table 4, which compares the survival observed in both the exploratory and test samples in relation to each of the four best prognostic factors. Clear differences in survival in relation to each clinical variable are as evident in the test sample as in the exploratory one, despite the smaller number of patients in the latter. This should demonstrate that the choice of these prognostic factors reflects the nature of the disease and its impact on the host rather than statistical chance.

Furthermore, when survival curves were analyzed for each unfavorable prognostic factor, no clear differences in discriminatory ability emerged among factors in either the exploratory or the test sample, and a clear grading of their prognostic severity could not be designed. Therefore, a regrouping of parameters would seem most suitable for clinical use. Use of slightly adjusted cutoff levels for the quantitative variables, such as age and hemoglobin, was necessary to allow a more balanced division of the patient series without substantial damage to discriminatory ability: to this aim, the

### Table 1. Main Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population</th>
<th>Exploratory Sample</th>
<th>Test Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>144</td>
<td>90</td>
<td>54</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>1.09</td>
<td>1.05</td>
<td>1.16</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>61.4 (35-92)</td>
<td>59.8 (35-92)</td>
<td>63.9 (40-89)</td>
</tr>
<tr>
<td>Serum IgM (g/L) (range)</td>
<td>27.7 (10.5-69.3)</td>
<td>28.5 (10.5-69.3)</td>
<td>24.7 (11.0-55.5)</td>
</tr>
<tr>
<td>k/λ light chain ratio</td>
<td>4.7</td>
<td>4.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Presence of urinary light chain (%)</td>
<td>41</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Marrow lymphoid cells (%)</td>
<td>54.4 (30-95)</td>
<td>55.5 (30-95)</td>
<td>52.5 (30-90)</td>
</tr>
</tbody>
</table>

**RESULTS**

Figure 1 shows the very similar survivals recorded in the exploratory sample and in the test sample, thus demonstrating the complete comparability of the two randomly chosen subsets of patients.

Table 2 illustrates the prognostic importance at univariate analysis of the clinical variables recorded at diagnosis in the 90 patients of the exploratory sample: these parameters are listed in descending order of statistical significance, and the quantitative ones are reported with the relatively best cutoff levels related to survival discrimination. As for platelet count it should be noted that although a cut-off value of $120 \times 10^9/L$ corresponds to the best pronosticator, statistically significant survival discrimination can be demonstrated all over the range between 110 and $180 \times 10^9/L$. Likewise, a clear statistical difference in survival is evident beginning at a cut-off value of 60 years of age.

Those variables that determined a fair discrimination of survival were selected for multivariate analysis. This included both variables that exceeded the standard limit of statistical significance (.05) and those that approximated it (.1 to .05). The results are reported in Table 3: only four clinical variables retained a statistically significant, independent prognostic role; moreover, a considerable gap in actual prognostic importance is clear between the first four and the remaining factors, which therefore can be discarded.

The validation of these results is demonstrated in Table 4, which compares the survival observed in both the exploratory and test samples in relation to each of the four best prognostic factors. Clear differences in survival in relation to each clinical variable are as evident in the test sample as in the exploratory one, despite the smaller number of patients in the latter. This should demonstrate that the choice of these four prognostic factors reflects the nature of the disease and its impact on the host rather than statistical chance.
best adapted levels proved to be 60 years for age and 10 g/dL for hemoglobin.

In the exploratory sample (see Fig 2) the clearest separation in survival outcome was obtained when two distinct groups of patients were compared, the first of whom presented no more than one negative parameter and the second consisted of patients with any two or more of the four unfavorable factors. Once again the goodness of fit to the data of this dichotomic prognostic discrimination was confirmed in the test sample, in which the difference between the favorable and unfavorable groups was still statistically significant, as shown in Fig 3.

The independency and the clinical relevance of each factor in relation to age, a characteristic which often limits therapeutic choices, are illustrated in Fig 4. In the whole series 64 patients were younger than 60 years, and the 15 with no more than one unfavorable factor (of the 3 remaining after the exclusion of age) clearly did worse than the other 49 with at least two unfavorable parameters. Of the 80 subjects over 60 years old, the 33 with no further unfavorable factors besides age showed significantly better survival than the remaining 47 with at least one other negative parameter.

**DISCUSSION**

To date, a great deal of interest has been focused on the clinical criteria for differentiating WM from its benign IgM-MGUS counterpart, from IgM multiple myeloma, other B lymphocyte neoplasias with a monoclonal IgM component, from chronic cryoagglutinin disease, and from cryoglobulinemia. The greatest challenge for clinical investigators is to distinguish between WM and IgM-MGUS, which is a particular aspect of the more general distinction between myelomatosis and benign monoclonal gammapathy. If cri-

![Fig 1. Comparison of the overall survival recorded in the two subsets of patients—(■) exploratory sample (90 patients) and (○) test sample (54 patients)—into which the total study population was randomly divided for statistical analysis and subsequent validation of results.](image-url)
Table 4. Comparison of the Survival Times Recorded in the Exploratory Sample (90 Patients) and in the Test Sample (54 Patients) in Relation to the Levels of Each of the Four Prognostic Parameters Selected by Multivariate Analysis

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Exploratory Sample</th>
<th>Test Sample</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75°</td>
<td>50°</td>
<td>25°</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;9 g/dL</td>
<td>35</td>
<td>78</td>
<td>129</td>
</tr>
<tr>
<td>&lt;9 g/dL</td>
<td>14</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>41</td>
<td>85</td>
<td>137</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>4</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>40</td>
<td>78</td>
<td>—</td>
</tr>
<tr>
<td>Present</td>
<td>23</td>
<td>38</td>
<td>92</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>35</td>
<td>85</td>
<td>137</td>
</tr>
<tr>
<td>Present</td>
<td>15</td>
<td>47</td>
<td>86</td>
</tr>
</tbody>
</table>

Lower quartiles, medians and upper quartiles of the observed survival times (in months) are given with the results of the log-rank test for each comparison.

teria were available for differentiating monoclonal processes destined to remain benign from those with a tendency to late malignant behavior, we could easily separate IgM-MGUS from WM. In this case, within the clinical spectrum of a sharply defined WM, we should search for further differences between an indolent phase of WM, not requiring treatment, and the clinically overt disease. At present, however, if a true indolent WM existed it has been included with IgM-MGUS, since it is easier to decide when a patient has to be treated or not, rather than to foresee if and when a benign monoclonal process will begin to behave like a malignancy.

As is well known, no "tests" are available that can immediately establish a differential diagnosis between IgM-MGUS and WM, despite the large series of criteria proposed: a serum concentration of the monoclonal IgM component higher than 10 g/L[10,20] or higher than 22.7 g/L[21]; the percent of J chain-positive bone marrow B cells[22,23]; serum β2-microglobulin levels lower than 3 mg/L[24]; lymphoid cell concentration higher than 20% of nucleated bone marrow cell[25-28] (though it is known that even less than 10% marrow infiltration can be recorded in early WM[22]); a threshold value over 0.25 of the discriminant function that takes into account the percentage of bone marrow lymphoid cells, the monoclonal fraction of the IgM-containing bone marrow cells, the total serum protein concentration, and the monoclonal component as percent of total serum protein.29 In fact, none of these criteria has proved to be reliable for differentiating between a patient affected with WM and one with its benign monoclonal counterpart.6 To do this at present the most reliable criterion is to monitor the IgM concentration over time and serially reevaluate clinical and laboratory features such as symptoms, possible complications, levels of normal polyclonal immunoglobulins, the presence and amount of Bence-Jones proteinuria, the number of lymphoid cells in the bone marrow, and serum β2-microglobulin levels.6

In the light of these facts the diagnosis of overt WM made in the patients of this study was based on both clinical and
laboratory findings. We disregarded any absolutely high amount of serum IgM, proven to be an unreliable discriminator except at low levels (a serum IgM concentration <10 g/L would indicate MGUS with very high probability\(^7\)), while we considered unequivocally demonstrated monoclonality to be the first requirement. Lymphoid cell infiltration of bone marrow also had to be greater than 30% of nucleated elements, a level decidedly higher than that used by other investigators\(^{25,27}\) in order to minimize possible misdiagnosis of cases with IgM-type MGUS as WM. However, the criterion that therapy had to be started within 6 months of diagnosis, as requested in the present study, represents the crucial parameter for diagnosis of overt WM and discriminates it from MGUS\(^1,7\).

In recent years the pathophysiologic mechanisms responsible for the variable clinical manifestations of WM have been largely investigated and reviewed\(^4\). A knowledge of the many clinical disorders that are a result of the physico-chemical or antibody properties of IgM molecules, or that stem from complex protein-protein or protein-cell interactions is important both at the onset of the disease (for quick selection of the clinical investigations that will lead to the correct diagnosis), and in the period preceding the final phase of the illness (since most of the life-threatening complications are an amplification of these pathophysiologic mechanisms no longer controlled by therapy).

Regarding the prognosis of WM, the only available results from multivariate analysis are those by Facon et al\(^12\), who found that male sex, neutrophil count <1.7 \(\times\) 10\(^9\)/L, age \(\geq\) 60 years, and hemoglobin <10 g/dL were the only factors independently related to survival. These results agree with ours only as far as the roles of age and hemoglobin are concerned. Discrepancies regarding the importance of the other two prognostic factors are probably due to different criteria adopted in the selection of cases. As a matter of fact, in Facon et al’s series, 39 of the 167 patients remained untreated, a condition suggesting they should have been considered as having MGUS rather than WM\(^7\). The favorable
fate of these patients, who represent 25% of all cases, may have influenced the results of the analysis.

The same bias affects all other studies dealing with the prognosis of WM. In particular, the only study in the 80's was that of Bartl et al., who found that pattern, histomorphometric volume, and histologic features of bone marrow infiltration were correlated with survival; moreover, they demonstrated that the three identified patterns of infiltration were correlated with cytologic and histologic features, ie, good correspondence was seen between nodular, interstitial/nodular, packed marrow patterns, and lymphoplasmacytic, lymphoplasmacytic, and polymorphous subtypes, respectively. Unfortunately, 58 of the 137 patients in their series either suffered from benign monoclonal gammopathy or from non-secretory immunocytoma, conditions that are not lymphoplasmacytic, and polymorphous subtypes, respectively. In our study, the classification of histologic features, which was preferred to evaluation of lymphoid infiltration patterns because of the greater confidence it afforded our pathologists, showed even less importance on survival, when univariately evaluated, than the percent amount of lymphoid infiltration. Thus, both were excluded from multivariate analysis.

A brief review of the clinical parameters that seemed to be important for survival at univariate analysis in less recent studies is available in Facon et al.'s work. Response to chlorambucil26 as a potential discriminator of survival was ignored in the present study, since we believe that a good prognostic factor must, if possible, guide therapeutic choice rather than depend on it a posteriori.

Few studies dealing with treatment of WM have been published. Standard criteria for therapy are still lacking, both because of the rarity of the disease, with the consequent difficulty in collecting sufficient numbers of prospective patients, and because of the variety of diagnostic criteria chosen in the series, which have been studied with regard to therapy. So, treatment is still largely empirical. In the majority of cases the treatment of choice is single-drug chemotherapy with an alkylating agent, mainly chlorambucil or melphalan; sometimes cyclophosphamide is preferred for its lower toxicity on platelets. In patients with severe symptoms due to hyperviscosity or the presence of cryoglobulins, alkylating agent chemotherapy is preceded, or accompanied early, by plasmapheresis. The results from small series of patients treated with multiple drug chemotherapy30,31 are promising, even though their true impact on survival is still controversial because WM patients are prone to the complications of heavy chemotherapy. A considerable risk of secondary acute leukemia is associated with both disease-related immunodeficiency and chemotherapy.32 Interferon has been found to obtain encouraging results33-34; however, optimal timing, dosage, and length of this therapy must still be defined.

We believe that our results can be useful for choosing treatment in clinical practice and for planning, or evaluating, clinical trials. It is likely that single-drug chemotherapy or interferon represents reasonable treatment for the group of WM patients over 60 years of age presenting with a favorable clinical picture, since such patients actually do well with single-drug chemotherapy (see Fig 4) and often are not good candidates for more aggressive therapy simply because of their advanced age. Multiple drug chemotherapy or investigational therapies seem to be indicated at least in the less favorable group of younger patients, in whom a shorter life expectancy makes development of a secondary neoplasm less likely in terms of time, and nearly negligible as far as an evaluation of death risks is concerned.

The criteria that discriminate these two prognostically different populations are quite simple and unequivocable. It is worth noting that the nature of some of the considered prognostic factors, such as age, weight loss, and hemoglobin level, are common to those used in the clinical evaluation of non-Hodgkin lymphomas. This is consistent with the basic consideration that WM is a B-lymphoproliferative disease, not distinguishable otherwise except for the presence of the IgM monoclonal component and its clinical consequences. It is more difficult to explain the unfavorable role of cryoglobulinemia, which, according to present data, proved to be independent of serum creatinine and renal failure. One can hypothesize that the appearance of cryoglobulinemia in the course of WM corresponds to the differentiation and expansion of a new cell subclone, different from the original and possibly able to justify the worsening of prognosis, as has been during the clinical progression of many CD5-positive B-cell neoplasms.35

In conclusion, we have clarified that WM, once it becomes clinically overt and begins to require treatment, presents at least two possible prognostic classes that can be identified very easily and inexpensively, and which should be taken into consideration both for choosing therapy and for designing future clinical trials or evaluating their results.

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Study of prognosis in Waldenstrom's macroglobulinemia: a proposal for a simple binary classification with clinical and investigational utility

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