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Prognostic Factors in Multiple Myeloma: a New Staging System Based on Clinical and Morphological Features

Paolo Pasqualetti, Raffaele Casale, Antonio Collacciani and Domenico Colantonio

A new staging system for multiple myeloma based on clinical and morphological features has been developed on the analysis of 190 patients. A score of "1" was assigned to each of the following clinical data, referred at the time of diagnosis, and selected by multivariate analysis: bone marrow plasma cells more than 30%, haemoglobin less than 110 g/l, lytic bone lesions of degree 2 or 3, serum β_2-microglobulin levels higher than 678 nmol/l, and presence of Bence–Jones proteinuria. Therefore, the score for each patient ranged from 0 to 5, and three clinical stages were provided: I = 0 or 1, II = 2 or 3 and III = 4 or 5. Substratification into A and B for each clinical stage was performed using multiple myeloma cellular score, calculated by the formula: total bone marrow myeloma cells per 500 cells × 0.752 + bone marrow plasmablasts per 500 cells × 0.709. Substage A corresponded to multiple myeloma cellular score value lower than 0.300, and substage B to a value greater than 0.300. Significant differences were found in median survivals ($P < 0.0001$), in survival curves ($P < 0.0001$), and in responses to treatment ($P < 0.0001$) among the six staged groups. The use of this staging system for multiple myeloma could offer new prognostic information and could better quantify the picture of the disease in each patient. The substaging according to morphological criteria seems very useful in diminishing or eliminating the great prognostic variability observed within the same clinical stage. Confirmatory studies are required to validate this new staging system for multiple myeloma.
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INTRODUCTION

STAGING IS a fundamental prerequisite to optimise therapeutic approach, and to estimate survival in various neoplasias. This is particularly true for some malignant diseases, such as multiple myeloma (MM), that presents a very heterogeneous clinical and biological course, survival ranging from less than 1 month to more than 10 years, and clinical course ranging from the relatively "indolent" form to aggressive neoplasia [1].

In the last years, several staging systems, based on clinical features [2–11] or on morphological criteria [12–17] have been proposed for MM, in order to facilitate the prognostic categorisation of patients, to improve treatment and to evaluate the effects of different therapeutic protocols. However, a great variability in survival of patients allocated to the same clinical or morphological stage has been observed [1, 8–10, 18, 19]. These findings have suggested the need to search for new parameters that will allow better individual control and evaluation of each patient.

The aim of the present study was to develop a staging system for MM that considered both clinical and morphological data, and to verify whether morphological subclassification could be useful in separating groups of clinically staged MM patients.

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PATIENTS AND METHODS

Patients, diagnostic criteria and treatment

A total of 190 patients, 111 men and 79 women (M/F = 1.4/1), ages ranging from 43 to 82 years (mean [S.D.] = 67 [8]), diagnosed as MM according to the criteria of the Southwest Oncology Group [20] were evaluated. There were 116 cases of MM IgG (75 IgG kappa and 41 IgG lambda), 42 cases of MM IgA (23 IgA kappa and 19 IgA lambda), and 32 cases of micromolecular MM (19 type kappa and 13 type lambda); 123 patients presented with Bence–Jones proteinuria.

At the time of first diagnosis, no patient had received specific treatment for MM. Considering the stage of disease and the general conditions of the patient, each case was treated with a specific treatment protocol, usually consisted of an intermittent course of alkylating agents and prednisone, with or without any other antineoplastic drugs. Therapy was continued until complete remission (CR) or partial remission (PR) was achieved. In the case of no response to therapy (NR), as well as in relapse, the choice of therapy was open, but usually consisted of a combination of chemotherapeutic drugs and prednisone. The response to therapy was evaluated according to the quantitative criteria of the Southwest Oncology Group [21], since in each case the myeloma cell mass (MCM) was calculated before and during treatment, using a programmable pocket calculator T.I.59 [22]. CR was defined as reduction of initial MCM of more than 75%, PR as reduction of initial MCM between 50% and 75%, and NR as reduction of initial MCM less than 50%.

Staging system

As previously reported [11], among 21 different prognostic indicators, Cox's model [23] selected from 121 patients with MM five highly significant prognostic variables: bone marrow plasma cell (BMPC) percentage, haemoglobin level, degree of lytic bone lesions, serum levels of β_2-microglobulin, (β_2M) and presence of Bence–Jones proteinuria. The score of "1" was assigned to each of the following clinical data, referred at the time of diagnosis: (a) BMPC more than 30%; (b) haemoglobin less than 110 g/l; (c) lytic bone lesions of degree 2 (multiple lytic bone lesions) or 3 (advanced multiple bone lytic lesions and/or pathological fractures); (d) serum levels of uncorrected β_2 M more than 678 nmol/l (8 μg/ml); (e) presence of Bence–Jones proteinuria. Therefore, the score for each patient ranged from 0 to 5. Three clinical stages were provided: stage I (good prognosis) = score 0 or 1; stage II (intermediate prognosis) = score 2 or 3; and stage III (poor prognosis) = score 4 or 5. See Appendix for examples of classification.

Our multiple myeloma cellular score (MMCS) [17] was employed for the substaging according to morphological criteria. The calculation of MMCS that uses the coefficients of correlation obtained using the Cox's proportional hazard regression model is the following: (0.752 × total bone marrow myeloma cells per 500 cells) + (0.709 × bone marrow plasmablasts per 500 cells). Plasmablasts were defined as bone marrow cells with an immature centrally located large nucleus with several nucleoli, and a relatively small light blue rim of cytoplasm.

The discriminative value for substaging was defined at the median value for the whole group of 0.300 of MMCS.

Statistical analysis

Survival time was measured in months from the time of first diagnosis, and, consequently, from the time of starting therapy until the time of death or that of closing the study. Early deaths were also included and 54 patients (28.4%) are still alive.

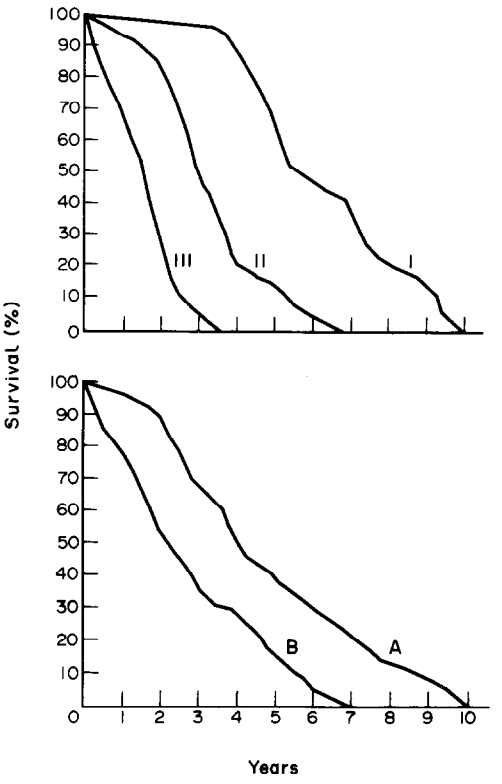

Fig. 1. Upper: Actuarial survival curves of the 190 patients with multiple myeloma subdivided into the three clinical stages. χ^2=102.3, P<0.0001. Lower: Actuarial survival curves of the same patient group subdivided into the two morphological stages. χ^2=37.4, P<0.0001.

The median survivals for each staged groups were calculated and compared by means of Quenouille's method [24]. Actuarial survival curves were computed by the Kaplan–Meier method [25], and compared using the logrank test [26]. The responses to therapy were also considered and compared using the χ^2 test [27].

RESULTS

The median (S.D.) survival of the whole group of MM patients was 31 (20) months. The median survival of the 65 patients (34.2%) with CR was 72 (30) months, of the 69 patients (36.3%) with PR was 38 (20) months and of the 56 cases (29.5%) with NR was 18 (10) months. This difference in median survivals was significant ($P < 0.001$).

There were statistically significant differences among the three clinical stages regarding median (S.D.) survivals [stage I = 67 (27) months, stage II = 36 (16) months, stage III = 18 (10) months; $P < 0.0005$), responses to treatment ($P < 0.0001$), and survival curves ($P < 0.0001$)], illustrated in Fig. 1.

The morphological staging based on MMCS has also divided the whole group into two subgroups with significant differences in median survivals [stage A = 47 (21) months, stage B = 27 (14) months; $P < 0.01$], in responses to treatment ($P < 0.005$), and in survival curves ($P < 0.0001$), illustrated in Fig. 1.

When the clinical stages were subdivided according to the morphological criteria, significant differences were found in median survivals ($P < 0.0001$), in response to chemotherapy ($P < 0.0001$) and in survival curves ($P < 0.0001$), illustrated in Fig. 2. Table 1 reports the median survivals and the responses to therapy in the six staged groups resulting from the staging system. Significant differences were also demonstrated between

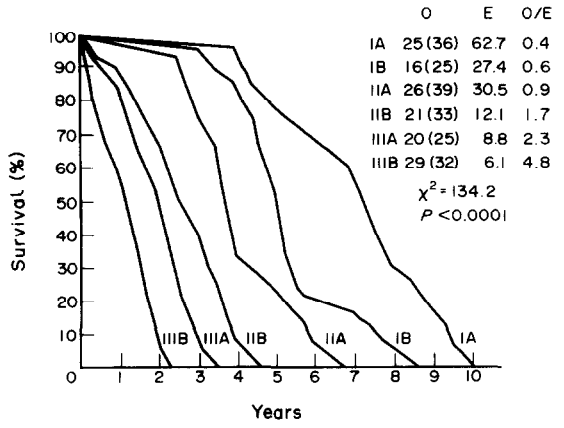

Fig. 2. Actuarial survival curves of 190 patients with multiple myeloma subdivided according to the new staging system based on clinical and morphological features. O=observed, E=expected. IA vs. IB: χ^2=8.8, P<0.05; IIA vs. IIB: χ^2=13.8, P<0.0005; IIIA vs. IIIB: χ^2=10.8, P<0.05.

the substage of each stage regarding median survivals ($P < 0.05$), and response to treatment ($P < 0.05$) except stage IA vs. stage IB.

DISCUSSION

We have recently proposed two different staging systems for MM, the first based on clinical features [11] and the other on exclusively morphological criteria [17]. Both staging systems are capable, at least in our series, of separating groups of MM patients with significant differences in survival and response to treatment. However, we have noted a great variability regarding prognoses in the same clinical or morphological stage. These results, as well as those regarding other staging systems [1, 8–10, 18, 19] could be due to the independent evaluation of clinical and morphological data. The previous clinical staging systems [2–11] have been proposed for different purposes and under different perspectives, and the use of one instead of another depends on the type of information being sought, and, moreover, by the availability of specific clinical data. On the other hand, the morphological classifications for MM [12–17], indicating that the plasmablast type of MM is associated with a poor prognosis [19], have considered only cellular criteria, independent of clinical data.

These limitations are the causes for which no single staging system in MM is generally adopted [1], demonstrating the necessity to define prognostic subgroups of patients on the basis of other data, especially serum β_2 M levels [28] or bone marrow myeloma cell infiltration [14]. We feel that our staging system, based on the simultaneous analysis and on the interdependence of clinical and morphological data, responds to this necessity. At present, none of the previous clinical stagings [2–10] considers the serum β_2-M levels, and only the scoring staging system proposed by Ludwig and Fritz [7] considers clinical data (haemoglobin and serum calcium) together with morphological features (total bone marrow myeloma cells infiltration and plasmablasts percentage), without substratification.

The most commonly employed method for considering the simultaneous effect of different variables on survival, which facilitates the grouping of patients according to the real major prognostic features, is the stepwise proportional hazard regression model of Cox [23]. In fact, using this method in our series, we have selected the most significant prognostic clinical features, and we have found the correlation coefficients for the morphological substaging. Since the subdivision of patients according to the parameter value requires arbitrarily defined cut-off points, and it is necessary that they split the series into groups of approximately equal size to be statistically helpful [1], the cut-off points established for the clinical system and for the substratification according to the morphological system were extrapolated by the median value of each variable for the whole MM patient group. While the clinical data employed in the clinical staging system are actually routine in the study of a patient with MM; used also for diagnosis, morphological criteria could be of a non-simple execution and reliability. On the other hand, cellular morphology of neoplastic myeloma cells could add a new dimension to prognosis that was largely independent of the clinical parameter [14, 17] and the identification and establishment of tumour-specific prognostic factors other than

Table 1. Median survivals and responses to chemotherapy in the six staged groups of multiple myeloma patients

Stage	Cases*	Median survival (mo)†	P	Response to therapy* CR	PR	NR	P
IA	36 [18.9]	86 (31)		24 [66.7]	10 [17.8]	2 [5.5]	
			< 0.05				> 0.05
IB	25 [13.2]	60 (23)		15 [60.0]	7 [28.0]	3 [12.0]	
IIA	39 [20.5]	44 (19)		12 [30.8]	18 [46.1]	9 [23.1]	
			< 0.05	< 0.0001			< 0.05 < 0.0001
IIB	33 [17.4]	29 (13)		7 [21.2]	12 [36.4]	14 [42.4]	
IIIA	25 [13.2]	21 (11)		5 [20.0]	11 [44.0]	9 [36.0]	
			< 0.05				< 0.05
IIIB	32 [16.8]	13 (10)		2 [6.2]	11 [34.4]	19 [59.4]	
All cases	190 [100.0]	31 (20)		65 [34.2]	69 [36.3]	56 [29.5]	

* No. [%].
† Mean (S.D.).
CR = complete remission, PR = partial remission, NR = no response.

the monoclonal component on a morphological basis could help eliminate or diminish the prognostic variability in the same clinical stage [14, 17]. In effect, this integrated staging system seems capable of identifying subgroups of patients allocated to the same clinical stage with different prognoses and responses to therapy; this seems especially valid for the patients allocated to clinical stage II, who are subdivided into two subgroups, of which stage IIA has those with prognosis similar to those in stage IB, and stage IIB with prognosis similar to stage IIIA. This fact could be very important in the therapeutic approach in the intermediate stage. The use of our MMCS, based only on a differential count of BMPC, without specific and sophisticated morphological and cytological studies, seems to be very valid. Moreover, we have assigned an optimal weight to myelomatous cell categories by the use of the coefficients obtained by the multivariate analysis, and in the formulation of clinical staging, we have attempted to emphasise the interdependence of the prognostic variables, giving each the same score, without attributing special importance to one over the others. No different staging systems have been developed for each immunological subtype of MM—even though they show different behaviour in tumour growth, synthesis rate, fractional catabolic rate and response to therapy [29, 30]—in order to avoid more complex calculations.

In conclusion, based on present data, we believe that the use of a staging system for MM that considers both clinical and morphological data, could better quantify the disease, since all aspects of MM are taken into account; and could offer new prognostic information in each MM patient. Confirmatory studies are required, however, to validate this new staging system.

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APPENDIX

Calculation of stage

The following example demonstrates the steps of prognostic evaluation of a patient with multiple myeloma at the time of diagnosis.

(1) Clinical parameters

(a) Bone marrow myelomatous cells: 45%	= score 1
(b) Haemoglobin: 115 g/l	= score 0
(c) Skeletal survey: multiple lytic bone lesions	= score 1
(d) Serum β_2-microglobulin levels: 932 nmol/l	= score 1
(e) Bence–Jones proteinuria: present	score 1
total score	= score 4

The patient is assigned to clinical stage III (poor prognosis).

(2) Morphological criteria:

(a) Differential count of the bone marrow smear yielded on 500 consecutive cells
Total myelomatous cell infiltration: 225
Plasmablasts: 55

(b) calculation of multiple myeloma cellular score (MMCS):
MMCS = (225/500) × 0.752 + (55/500) × 0.709 = 0.416.

The patient is assigned to morphological substage B (more than 0.300).

The staging system places the patient into stage IIIB.