Eur J Cancer, Vol. 27, No. 11, pp. 1401–1405, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Changing Clinical Presentation of Multiple Myeloma

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We compared the presentation features of three series of patients with multiple myeloma diagnosed between 1960 and 1971 (Kyle R, *Mayo Clin Proc*, 1975, 50, 29, $n = 869$), 1972 and 1986 (Clinica Medica, University of Pavia, $n = 345$) and 1987 and 1990 (Cooperative Group for Study and Treatment of Multiple Myeloma, $n = 341$). In the most recently diagnosed patients, the percentage of those who had symptoms related to multiple myeloma (i.e. any of bone pain, systemic symptoms, disturbances related to hypercalcemia, neurological involvement and hyperviscosity) was reduced (90 vs. 86 vs. 66%) ($P < 0.001$), while the percentage of asymptomatic patients diagnosed by chance was increased (not reported, and 14 vs. 34%). In the most recent series, a lower percentage of spontaneous bone pain (68 vs. 60 vs. 37%, $P < 0.001$) paralleled a lower incidence of advanced bone disease (osteolyses and pathological fractures, 60 vs. 64 vs. 34%), and renal failure (serum creatinine > 1.2 mg/dl) was also less common (56 vs. 44 vs. 33%, $P < 0.01$), at least partially due to a decreased incidence of both hypercalcemia (30 vs. 20 vs. 18%, $P < 0.001$) and of hyperuricemia (serum uric acid > 7 mg/dl, 47 vs. 32 vs. 26%, $P < 0.01$). Systemic symptoms (weakness, infections, fever or weight loss) were reported more seldom by recently diagnosed patients, due to a decreased frequency of anaemia (haemoglobin < 12 g/dl), leukopenia and thrombocytopenia, as well as of the systemic effects of bone pain and of renal insufficiency. These data indicate that multiple myeloma is diagnosed earlier now than in the past, and this must be taken into account when comparing survival data in treated series.
Eur J Cancer, Vol. 27, No. 11, pp. 1401–1405, 1991.

INTRODUCTION

BONE PAIN (with systemic symptoms often associated), multiple X-ray osteolyses and a monoclonal component on serum protein electrophoresis are the essential features of multiple myeloma. All of them were almost universally found in patients diagnosed some decades ago, when this neoplasm was considered one of the most painful and invalidating diseases [1].

The thorough medical care available at present, besides increasing the frequency of diagnoses of multiple myeloma [2, 3], is also expected to allow earlier detection of the disease, since both radiology (for osteoarthritis and other rheumatic diseases) and blood examinations (for a variety of reasons, including routine blood evaluations in clinically asymptomatic individuals) are increasingly employed.

This is shown in the present report, where we compare the clinical, radiological and laboratory presentation features of three series of multiple myeloma collected in three subsequent time intervals: between 1960 and 1971, between 1972 and 1986 and between 1987 and 1990.

PATIENTS AND METHODS

This is an analysis of the major presentation features of multiple myeloma in three series of patients who sought medical assistance at a division of internal medicine or of haematology for a suspected diagnosis of this disease.

Diagnoses were made in three subsequent time intervals, starting from 1960. Series 1 was collected by Kyle between 1960 and 1971 and is already published [1]; series 2 was a retrospective series collected at the Clinica Medica of the University of Pavia and includes patients diagnosed between 1972 and December, 1986; and series 3 included patients who entered a multicentre protocol for the study and treatment of multiple myeloma (coordinated at the Clinica Medica II of the University of Pavia and referred to as Multiple Myeloma Protocol 1987) between January 1987 and January 1990 [4].

Criteria for diagnosis

For series 1 and 2, clinical records of all patients with a diagnosis of multiple myeloma were obtained and reviewed. For series 3, the data at presentation of patients registered into Multiple Myeloma Protocol 1987 [5] were reviewed. This protocol enroled all patients diagnosed as having multiple myeloma at one of the participating centres. At time of this analysis (January 1990) 23 of 364 registered patients had been excluded after revision of patient's records by the coordinating centre: 13 had insufficient data for confirming the diagnosis of multiple myeloma while in 10 patients, the diagnosis was invalid for inclusion in the protocol (Waldenstrom macroglobulinemia: 1, primary amyloidosis. 2, monoclonal gammopathy of undetermined significance: 3 and cancer-associated osteolysis and associated monoclonal protein: 4 patients).

Criteria for diagnosing multiple myeloma were basically the

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Received 13 June 1991; accepted 17 July 1991.

same for the three series. Diagnosis required the presence of at least two of the following signs: (a) a monoclonal component in the serum and/or urine; (b) multiple osteolytic bone lesions; or (c) an increase in bone marrow plasma cell infiltrate. For series 1 and 2, bone marrow plasma cell (BMPC) greater than 5% [1] and 10%, respectively had to be found on a bone marrow aspirate. For series 3, bone marrow plasma cell greater than 20% had to be ascertained on a threphine biopsy [5]. In series 3, a biopsy of a lytic lesion showing plasma cell infiltration was required for the diagnosis of non-secretory multiple myeloma [i.e. patient fulfilling criteria (b) and (c) only].

Excluded from the analysis were patients with monoclonal gammopathy of undetermined significance (these patients had serum and/or urine monoclonal component but had no osteolyses, and their BMPC was less than 5, 10 and 20% in series 1, 2 and 3, respectively), reactive marrow plasmocytosis (e.g. rheumatoid arthritis, chronic infections, collagen disease, carcinoma, lymphoma or leukaemia, aplastic anemia), solitary osseous or extramedullary plasmocytoma and primary plasma cell leukaemia.

Data recording

869 patients were evaluable in series 1, 345 in series 2 and 341 patients in series 3. Table 1 lists the parameters taken into consideration, along with the numbers and percentages of patients of each series who had available data.

In series 2 and 3, skeletal X-ray lesions were graded according to criteria employed in series 1 [1]: grade 0 = normal bone appearance; grade 1 = diffuse osteoporosis; grade 2 = osteolyses only; grade 3 = pathological fractures only or simultaneous osteolyses and pathological fractures. Patients of series 2 and 3 were also staged according to Durie and Salmon [6] (for this purpose the skeletal X-ray picture was graded according to this staging system). A number of them had special investigations available, including the levels of serum β2-microglobulin [7] and of thymidine kinase [8] (in series 2 this enzyme was determined on sera stored at −20° for 3–12 years and in series 3 it was determined on fresh sera), DNA flow cytometry (for DNA ploidy) [9] and the *in vitro* tritiated thymidine labelling index of bone marrow plasma cell [10].

Statistical analysis

Single data distribution was available for series 2 and 3, while in the paper describing series 1 the population's features are reported more often as percentages of patients with the same clinical and/or radiological and/or laboratory characteristics (and as mean value for the whole population for BMPC%, monoclonal component level and erythrocyte sedimentation rate). Hence, differences among series 1, 2 and 3 in the frequency of patients having the same clinical, radiological or laboratory characteristics were evaluated using contingency tables and χ^2 test.

For quantitative variables which were available in series 2 and 3 (namely, daily calciuria and hydroxyprolinuria, β2 microglobulin and thymidine kinase levels, DNA ploidy and BMPC labelling index) the comparison of means was made by two-tailed Student's *t* test.

RESULTS

Table 2 summarises the presentation features of patients with multiple myeloma included in the three series we compared. The clinical, radiological and laboratory data were arranged cumulatively, as much as possible, concerning the involvement of the single organs or organ systems.

Table 1. Available clinical, radiological and laboratory data from three series of patients with multiple myeloma diagnosed between 1960 and 1990

Parameter	Evaluable patients		
	Series 1 (1960–1971)	Series 2 (1972–1986)	Series 3 (1987–1990)
No. of patients	869 (100)	345 (100)	341 (100)
Age	869 (100)	345 (100)	341 (100)
Sex	869 (100)	345 (100)	341 (100)
History	869 (100)	345 (100)	341 (100)
Physical examination	869 (100)	345 (100)	341 (100)
Skeletal X-ray	824 (94)	257 (75)	341 (100)
Serum calcium	611 (70)	274 (79)	312 (91)
24-h calciuria	NA	72 (20)	239 (70)
24-h hydroxyprolinuria	NA	73 (20)	246 (72)
Serum alkaline phosphatase	336 (38)	241 (70)	288 (84)
Bone marrow aspiration	799 (92)	320 (93)	316 (92)
Bone marrow biopsy	NA	72 (21)	284 (83)
Haemoglobin	741 (85)	339 (98)	341 (100)
Platelets	543 (62)	345 (100)	341 (100)
Leucocytes	737 (85)	330 (95)	341 (100)
Serum albumin	727 (83)	306 (88)	341 (100)
Serum creatinine	389 (45)	293 (85)	341 (100)
Serum uric acid	489 (56)	249 (72)	309 (90)
Stage (DS)	NA	314 (91)	341 (100)
Serum electrophoresis	537 (62)	345 (100)	341 (100)
Light chains	533 (61)	345 (100)	341 (100)
Bence–Jones proteinuria	320 (37)	129 (37)	295 (86)
Plasma viscosity	80 (9)	128 (37)	177 (52)
ESR	727 (84)	306 (88)	341 (100)
β_2-microglobulin	NA	105 (30)	246 (72)
Thymidine kinase	NA	29 (8)	147 (44)
BMPC-LI	NA	47 (13)	125 (37)
BM DNA FCM	NA	52 (15)	108 (32)

No. of patients (%).
1960–1971 = retrospective series from the Mayo Clinic [1]; 1972–1986 = retrospective series from the Clinica Medica of the University of Pavia; 1987–1990 = prospective series from the Cooperative Group for the Study and Treatment of Multiple Myeloma [4]; NA = not available; ESR = erythrocyte sedimentation rate at 1 h; DS = Durie and Salmon; BMPC LI = bone marrow plasma cell labelling index; BM DNA FCM = DNA flow cytometry of bone marrow plasma cells.

Age and sex

Median age (60–66 years) was similar in the three series. However, only about 3% in series 1 and 2, but 7% of patients in series 3 were younger than 50 years ($P < 0.001$). Patients older than 70 years were also more frequent in series 3.

The male to female predominance was reduced from series 1 (M/F = 1.56) to series 2 (M/F = 1.27) to series 3 (M/F = 0.97) ($P < 0.01$).

History

An average of 4–6 months elapsed from symptoms to diagnosis; 90, 86 and 66% of the patients in series 1, 2 and 3, respectively, ($P < 0.001$) had symptoms that were clearly related to multiple myeloma, i.e. bone pain or disturbances related to hypercalcaemia (from bone destruction) and/or systemic symptoms (including weakness from anaemia, fever from immunodepression, bleeding from thrombocytopenia or other coagulation abnormalities, and weight loss) and/or complaints due to neurological involvement and/or to hyperviscosity.

Table 2. Main clinical radiological and laboratory features at diagnosis of patients with multiple myeloma diagnosed between 1960 *and* 1990

Parameter at diagnosis	Time of diagnosis 1960–1971	1972–1986	1987–1990	*P*
No. of patients	869	345	341	–
Median age (yr) (%)	62	60	66	NS
< 40	0.5	1.5	1.0	NS
< 50	2.6	3.0	7.0	< 0.0001
> 50 and < 70 yrs	74.5	66.4	56.0	< 0.0001
> 70	23.0	18.3	37.0	< 0.0001
M/F (%)	61/39 (1.56)	56/44 (1.27)	49/51 (0.97)	< 0.01
History				
Months from symptoms to diagnosis, median	NA	5.5	4.5	NS
Symptomatic patients	90	86	66	< 0.001
Occasional diagnosis	NA	14	34	< 0.001
Immunochemical characteristics				
Serum MC, g/dl, mean	3.6	2.9	3.7	NS
MC type				
IgG	59	63	64	
IgA	23	21	23	
IgD	1	1	2	NS
IgM	–	–	0.2	
Light chain only	17	15.5	9	
Not secreting	NA	NA	1.5	
Type of light chain				
K	60	43	56	
L	30	30	36	< 0.01
Unknown	10	27	8	
B-J proteinuria	49	38	47	NS
Bone disease				
Spontaneous bone pain	68	60	37	< 0.001
Skeletal X-ray*				
Scale 0	21	15	27	
Scale 1	6	4	19	< 0.001
Scale 2	13	17	20	
Scale 3	60	64	34	
Serum calcium > nv	30	20	18	< 0.001
24 h calciuria, mg, mean	NA	321	201	NS
24 h OH-prolinuria, mg, mean	NA	79	48	NS
Alkaline phosphatase > nv	25	31	30	NS
Systemic symptoms	NA	82	31	< 0.001
Weakness	NA	65	42	< 0.001
Infection	12	10	12	NS
Haemorrhage	7	4	2	< 0.01
Weight loss	NA	12	11	NS
Haematological involvement				
Haemoglobin < 12 g/dl	62	61	39	0.01
Platelets < 100 × 10⁹/l	13	11	3	0.05
Leucocytes < 4 × 10⁹/l	16	5	7	0.05
BMPC%, mean	36	40	46	NS
Renal involvement				
Creatinine > 1.2 mg/dl	56	44	33	0.01
Creatinine > 2.0 mg/dl	29	14	10	0.01
Creatinine > 5.0 mg/dl	10	4	3	0.05
Neurological involvement	NA	NA	1.5	–
Organomegaly				
Hepatomegaly	21	30	32	0.01
Splenomegaly	5	3	2	NS
Lymphadenopathy	4	4	1	NS
Palpable abdominal mass	NA	2	2	NS
Miscellaneous laboratory features				
ESR first hour, mean	82	82	85	NS
Serum uric acid > 7 mg/dl	47	32	26	0.01
Serum albumin < 3 g/dl	52	21	7	0.001
Plasma viscosity > nv	89	87	55	0.001
Clinical stage (Durie and Salmon, 1975)				
Stage I	NA	12	23	
Stage II	NA	15	28	
Stage III	NA	73	49	0.01
Special examinations				
Serum β_2, μg/ml, mean	NA	6.5	6.0	NS
Serum TK, U/ml, mean	NA	4.2	9.7	0.001
BMPC LI, %, mean	NA	2.9	2.9	NS
Aneuploidy (DNA FCM)	NA	53	31	NS

* Scaling of X-ray skeletal lesions: scale 0 = no bone changes; scale 1 = diffuse osteoporosis; scale 2 = lytic lesions only; scale 3 = pathological fractures or simultaneous lytic lesions and pathological fractures. B-J = Bence–Jones; β_2 = β_2 microglobulin; TK = thymidine kinase; LI = *in vitro* labelling index; DNA FCM = DNA flow cytometry; MC = monoclonal component; OH-prolinuria = hydroxyprolinuria. Numbers are percentages of patients, unless otherwise stated.

In 14% of patients in series 2 but in 34% of those in series 3 ($P < 0.001$) the diagnosis of multiple myeloma was made by chance. In series 3, the overwhelming majority (88%) of occasional diagnosis was due to the chance finding of a serum monoclonal component on a blood examination made for reasons unrelated to multiple myeloma which led to further confirmatory investigations. The percentage of patients diagnosed by chance is not specifically reported for series 1.

Immunochemical characteristics

No clear change in the distribution of immunochemical characteristics (including Bence–Jones proteinuria) was seen among the three series. In series 3, 5 patients had non-secreting multiple myeloma, with multiple osteolytic lesions and > 70% plasma cells at the site of biopsy. The only one case of IgM monoclonal component accepted in series 3 as multiple myeloma was a 68-year-old male patient who presented with osteolyses and pathological fractures and > 80% atypical plasma cells in the bone marrow biopsy.

Bone disease

Spontaneous bone pain was the presentation complaint in 68 and 60% of patients in series 1 and 2, but only in 37% of those in series 3 ($P < 0.001$). Accordingly, extensive skeletal involvement (grade 3, i.e. pathological fractures only or simultaneous osteolyses and pathological fractures) was found in 60 and 64% of patients in series 1 and 2, but only in 34% of the patients in series 3 ($P < 0.001$). On the contrary, grade 0

(normal skeleton), 1 (osteoporosis) and 2 (osteolyses only) X-ray pictures were found more often in series 3 patients than in the older series ($P < 0.001$).

Other signs of bone resorption were also milder in the recently diagnosed patients. Hypercalcaemia was a presentation finding in 30% of series 1 patients, but only in 20 and 18% of series 2 and 3 patients ($P < 0.001$). The mean daily urinary excretion of calcium and hydroxyproline was also lower in series 3 than in series 2 patients, although the difference was not significant.

Systemic symptoms

Weakness and/or fever and/or bleeding disorders and/or weight loss were less frequent in series 3 (31% of patients) than in series 2 (82% of patients) ($P < 0.001$).

Haematological involvement

Anaemia (haemoglobin < 12 g/dl, usually normocytic) was less frequent in the recently diagnosed patients ($P < 0.01$). In these patients, leukopenia (leucocyte count $< 4 \times 10^9$/l) and thrombocytopenia (platelets $< 100 \times 10^9$/l) as well as bleeding disorders (but not documented infections), were also less common ($P < 0.05$ and < 0.01, respectively). The mean BMPC infiltration was similar in the three series.

Renal involvement

56% of patients in series 1 but only 44 and 33% of patients in series 2 and 3, respectively had serum creatinine levels > 1.2 mg/dl ($P < 0.01$). Patients with serum creatinine > 2.0 and 5.0 were also less frequent in series 3 than in 1 and 2 ($P < 0.01$ and < 0.05, respectively). Symptoms due to renal insufficiency (polyuria and/or polydipsia) were found in 7 and 10% of patients in series 2 and 3 (these data were not reported for series 1).

Neurological involvement

Data on neurological involvement are available only for series 3, where it was a presentation complaint in 5 (1.5%) patients. In all but 1 case neurological damage was represented by sensory loss and/or paresthesias. In the other patient, there was a rapid progressive loss of motor capacity of the leg muscles due to nerve root compression by an epidural mass.

Enlargement of organs

Liver enlargement (i.e. a palpable liver) was frequent (21–32% in all series, but its relationship to multiple myeloma was not ascertained. Enlargement of the spleen and lymph-nodes was uncommon (1–5% of patients); 2% of patients in series 2 and 3 had palpable abdominal masses, which turned out to be plasma cell neoplasms at biopsy and disappeared or were reduced with antineoplastic therapy.

Miscellaneous laboratory features

Median erythrocyte sedimentation rate was similar in all series. Hypoalbuminaemia was much less common in the more recent (21 and 7%, respectively) than in the oldest (52% of cases) series ($P < 0.001$).

Hyperuricaemia decreased from 47 (series 1) to 32 (series 2) and 26% (series 3) ($P < 0.01$).

An elevated plasma viscosity was found in 89 and 87% of series 1 and 2 patients, and in 55% of those in series 3 ($P < 0.001$). Symptomatic hyperviscosity syndrome was present in only 2 patients of series 3 (the IgG monoclonal component peak was 6.3 and 9.0 g/dl). Data on symptomatic hyperviscosity are not available for series 1 and 2.

Stage of disease

With respect to series 2, series 3 had more patients with early (stage I and II) than advanced (stage III) multiple myeloma ($P < 0.001$).

Special examinations

Serum thymidine kinase, but not β_2 microglobulin level was much higher ($P < 0.001$) in series 3 than in series 2 patients.

Aneuploid plasma cells on DNA flow cytometry were found in 53% of patients in series 2 and in 31% of those in series 3 (not significant). In both series the most frequent pattern was hyperdiploidy (only 1 patient in series 2 and 1 in series 3 had hypodiploid BMPC). BMPC labelling index was similar in both series 2 and 3.

DISCUSSION

In this analysis we have compared the major presentation features of three series of patients whose multiple myeloma was diagnosed over three subsequent decades. There were no strict guidelines for recruiting patients into these series, but entrance criteria can be accepted as sufficiently close. In fact, patients referred to internal medicine or haematology centres for a suspected myeloma (there was no recruitment from laboratory, nephrology or orthopaedic units) and criteria for diagnosis were both similar and reviewed before the analysis [1, 5].

Data indicate that the presentation of multiple myeloma is less dramatic now than 20–30 years ago, probably due to the greater availability of medical assistance [11, 12] which allows an earlier diagnosis.

A key point is that multiple myeloma is now diagnosed by chance in about one third of cases. These patients sought medical counselling not due to myeloma-related disturbances, but because they were found to have a serum monoclonal component on electrophoresis performed for unrelated reasons. Further investigations confirmed the diagnosis of multiple myeloma in these otherwise asymptomatic patients.

The lower incidence of bone disease, of renal involvement and of systemic symptoms are three additional changes in the clinical characteristics of multiple myeloma which point to a generally earlier diagnosis.

The decreased percentage of spontaneous bone pain parallels the lower incidence of advanced bone disease (osteolyses with pathologic fractures). Other haematochemical parameters related to bone disease (i.e. serum calcium level and 24 h excretion of calcium and hydroxyproline) were also lower in the recently diagnosed patients. In the more recent series, the BMPC% was also found to be a parameter strictly linked with bone disease [5]. Its median value has not changed over the years, probably due to the fact that the lowest BMPC infiltration required for diagnosis of multiple myeloma was much greater (20%) in series 3 than in the older series (5% in series 1 and 10% in series 2).

Renal involvement (both simply defined as a serum creatinine level > 1.2 mg/dl or as a more severe degree of renal failure) is now less common. This change is probably accounted for by the decreased incidence of both hypercalcaemia and hyperuricaemia (Bence–Jones proteinuria was found equally, independently of the time of diagnosis).

Systemic symptoms, including weakness, fever, bleeding disorders and weight loss were also much less frequent in the recently diagnosed patients. There are several causes for this decrease. Bone disease, haematological involvement (anaemia, leukopenia and thrombocytopenia) and renal insufficiency are

all reduced, together with their systemic effects. Hypoalbuminaemia, whose origin in multiple myeloma is poorly understood but which has a very poor prognostic significance in this disease [13], is also much less common. Yet the evaluation modality of some symptoms, such as weakness, may have played a role, in that retrospective data from series 1 and 2 were interpreted from clinical records, while in the prospective series 3, questions were asked directly to patients.

Despite the fact that the percentage of patients with leukopenia is decreased, documented infections were not reduced, probably due to the fact that leukopenia is not the only factor responsible for infections in untreated multiple myeloma (where immunological depression plays a major role) [14] and because diagnosis of infection is much easier now than in the past.

Additional findings from our analysis include the progressive decrease in male to female predominance (explanations could be that lifestyle changes expose women to the same environmental carcinogenic factors as men or that more women than men live to the older age, thus paralleling the increased incidence of multiple myeloma with age) and the percentage increase of patients less than 50 and, especially, over 70 years of age (possibly due to better medical attention for the elderly).

Since a number of the parameters considered above, namely skeletal X-ray, calcaemia, haemoglobin and creatinine, are used for staging multiple myeloma [6] and are less abnormal in present than in past patients, there is now a reduction in the incidence of advanced stage III multiple myeloma and a corresponding increase in stage I and II myelomas.

Earlier diagnosis should be accounted for when comparing survival data of multiple myeloma patients treated with chemotherapy in the past and now.

1. Kyle RA. Multiple myeloma: review of 869 cases. *Mayo Clin Proc* 1975, **50**, 29–40.
2. Devesa SS, Silverman DT. Cancer incidence and mortality trends in the United States: 1935–74, *J Natl Cancer Inst* 1978, **60**, 545–571.
3. Velez R, Beral V, Cuzick J. Increasing trends of multiple myeloma mortality in England and Wales: 1950–79. Are the changes real? *J Natl Cancer Inst* 1982, **69**, 387–392.
4. Riccardi A, Ucci G, Luoni R, Cassano E, Castello A, Ascari E, (for the Cooperative Group of Study and Treatment of Multiple Myeloma), eds. Multiple myeloma: a treatment program which includes stratification of patients into three disease stages and randomizations for both induction and maintenance therapy. In: Caronia F, Malleo C, Marcenò R, eds. "*Ematologia* '88", Bologna, Editoriale Grasso, 1990, 815–832.
5. Riccardi A, Ucci G, Luoni R, *et al.* (for the Cooperative Group of Study and Treatment of Multiple Myeloma). Bone marrow biopsy in monoclonal gammopathies: correlations between pathologic findings and clinical data. *J Clin Pathol* 1990, **43**, 469–475.
6. Durie BGM, Salmon SE. A clinical staging system for myeloma: correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 1975, **36**, 842–854.
7. Bataille R, Grenier J, Sany J. Beta-2-microglobulin in myeloma: optimal use for staging, prognosis, and treatment. A prospective study on 160 patients. *Blood* 1984, **63**, 468–476.
8. Ucci G, Riccardi A, Luoni R, *et al.* Serum thymidine kinase and beta-2 microglobulin in monoclonal gammopathies. *Tumori* 1987, **73**, 445–449.
9. Montecucco CM, Riccardi A, Merlini GP, *et al.*, Plasma cell DNA content in multiple myeloma and related paraproteinemic disorders. Relationship with clinical and cytokinetic features. *Eur J Cancer Clin Oncol* 1984, **20**, 81–90.
10. Riccardi A, Montecucco CM, Danova M, Ucci G, Merlini GP, Ascari E. Rate of M-component changes and plasma cell labeling index in 25 patients with multiple myeloma treated with Peptichemio. *Cancer Treat Rep* 1985, **69**, 971–975.
11. Cuzick J, Velez R, Doll R. International variations and temporal trends in mortality from multiple myeloma. *Int J Cancer* 1983, **31**, 13–19.
12. Turesson I, Zettervall O, Cuzick J, Waldenström JG, Velez R. Comparison of trends in the incidence of multiple myeloma in Malmö, Sweden, and other countries, 1950–1979. *N Engl J Med* 1984, **310**, 421–424.
13. Bataille R, Durie BGM, Grenier J, Sany J. Prognostic factors and staging in multiple myeloma: a reappraisal. *J Clin Oncol* 1986, **4**, 80–87.
14. Jacobson De, Zolla-Pazner S. Immunosuppression and infections in multiple myeloma. *Semin Oncol* 1986, **13**, 282–290.

Acknowledgements—This research was supported by CNR (Consiglio Nazionale delle Ricerche, Roma, Progetto Finalizzato Oncologia, grant no. 88.01422.44), by AIRC (Associazione Nazionale per la Ricerca sul Cancro, Milano), by IRCCS Policlinico San Matteo (Pavia) and by Fondazione Ferrata-Storti.

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