Original Article

Review of 1027 Patients With Newly Diagnosed Multiple Myeloma

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• ***Objective*: To determine the clinical and laboratory features of newly diagnosed multiple myeloma.**

• ***Patients and Methods*: Records of all patients in whom multiple myeloma was initially diagnosed at the Mayo Clinic in Rochester, Minn, from January 1, 1985, to December 31, 1998, were reviewed.**

• ***Results*: Of the 1027 study patients, 2% were younger than 40 years, and 38% were 70 years or older. The median age was 66 years. Anemia was present initially in 73% of patients, hypercalcemia (calcium level ≥11 mg/dL) in 13%, and a serum creatinine level of 2 mg/dL or more in 19%. The β_2-microglobulin level was increased in 75%. Serum protein electrophoresis revealed a localized band in 82% of patients, and immunoelectrophoresis or immunofixation showed a monoclonal protein in 93%. A monoclonal light chain was found in the urine in 78%. Nonsecretory myeloma was recognized in 3% of patients, whereas light-chain myeloma was present in 20%. Conventional radiographs showed an abnormality in 79%. The plasma cell labeling index was 1% or more in 34% of patients. Multivariate analysis revealed that age, plasma cell labeling index, low platelet count, serum albumin value, and the log of the creatinine value were the most important prognostic factors.**

• ***Conclusion*: The median duration of survival was 33 months and did not improve from 1985 through 1998.**

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AL = primary amyloidosis; MGUS = monoclonal gammopathy of undetermined significance; M-protein = monoclonal protein

Multiple myeloma (plasma cell myeloma, plasmacytic myeloma, myelomatosis, Kahler disease) is a neoplastic disorder characterized by proliferation of a single clone of plasma cells derived from B cells. This clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone, producing skeletal destruction that results in bone pain and fractures. Occasionally, plasma cells infiltrate multiple organs and produce other symptoms. The excessive production of a monoclonal protein (M-protein) may lead to renal failure from Bence Jones proteinuria or hyperviscosity from excessive amounts of M-protein in the blood. The diagnosis depends on identification of abnormal monoclonal plasma cells in the bone marrow, M-protein in the serum or urine, osteolytic lesions, and a clinical picture consistent with multiple myeloma.

Multiple myeloma accounts for about 1% of all types of malignancy and slightly more than 10% of hematologic malignancies. In the United States, the incidence of multiple myeloma increased from 0.8 per 100,000 population in 1949 to 1.7 per 100,000 in 1963 and to 3.5 per 100,000 for males and 3.1 per 100,000 for females in 1988.[1] In Olmsted County, Minnesota, the incidence was 3.1 per 100,000 from 1945 to 1964, 2.7 per 100,000 from 1965 to 1977, and 4.1 per 100,000 from 1978 to 1990.[2] The reported increased incidence during the past few decades is probably related more to the increased availability of medical facilities for elderly patients and to improved diagnostic techniques than to an actual increased incidence. Multiple myeloma occurs in all races, but rates are higher in African Americans and lower in Asian populations.

For editorial comment, see page 15.

Multiple myeloma has most likely been present for centuries, but the first well-documented patient, Sarah Newbury, was reported by Samuel Solley in 1844. Six years later, William Macintyre described the illness of Thomas Alexander McBean, who had severe bone pain and at autopsy was found to have cells in the bone marrow consistent with those of multiple myeloma. Macintyre noted that the urine was found to "abound in animal matter" when heated but it "underwent complete solution" when boiled and then reappeared on cooling. He sent a sample of the urine to Henry Bence Jones, a 31-year-old

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physician at St George's Hospital who had an established reputation as a chemical pathologist.[3] Bence Jones confirmed the findings of Macintyre and concluded that the protein represented a "deutoxide of albumen." However, Bence Jones recognized the importance of the protein when he stated, "I need hardly remark on the importance of seeking for this oxide of albumen in other cases of mollities ossium" [softening of the bone].[4]

The term *multiple myeloma* was introduced by J. von Rustizky in 1873, and 16 years later Otto Kahler described a case involving a 46-year-old physician, Dr Loos. He had an 8-year history of progressive pain, recurrent fractures, loss of height, and severe kyphosis. His bone marrow contained large cells consistent with myeloma, and his urine contained the typical protein as described by Bence Jones. As a tribute to Korngold and Lipari,[5] the 2 major classes of Bence Jones protein have been designated kappa (κ) and lambda (λ). J. H. Wright, who described the peripheral blood stain of the same name, noted that radiographs showed changes in multiple ribs of a patient with myeloma in 1898. He concluded that the bone marrow cells consisted of plasma cells or their immediate descendants. The tall, narrow-based "church spire" peak was noted on serum protein electrophoresis in 1939.[4]

In 1975, a review of 869 patients with myeloma seen at the Mayo Clinic from 1960 to 1971 described the clinical features and natural history of multiple myeloma.[6] That study was done at a time when there was limited information on prognostic factors and few therapeutic options besides melphalan and prednisone. More recently, investigators at the University of Arkansas described the natural history and outcome of large cohorts of patients with myeloma.[7,8] Their patients do not represent the full spectrum of myeloma but a selected group well enough to undergo 1 or 2 stem cell transplantations. Most other studies also have the drawback that the inception cohort does not represent all patients with a verified diagnosis of myeloma seen over a defined period. Furthermore, follow-up is often inadequate. The purpose of this study was to determine the natural history, clinical features, and outcome of newly diagnosed multiple myeloma in an accurately defined, large cohort of consecutive patients seen at the Mayo Clinic during a 14-year period.

PATIENTS AND METHODS

The records of all patients in whom multiple myeloma, plasmacytic myeloma, plasma cell myeloma, myelomatosis, or Kahler disease was initially diagnosed at the Mayo Clinic in Rochester, Minn, from January 1, 1985, to December 31, 1998, were reviewed. The diagnosis of multiple myeloma was based on the following findings: (1) increased numbers of abnormal, atypical, or immature plasma cells in the bone marrow or histologic proof of plasmacytoma; (2) presence of an M-protein in the serum or urine; or (3) bone lesions consistent with those of multiple myeloma. Patients with plasma cell reactions to connective tissue disorders, liver disease, metastatic carcinoma, or chronic infections were excluded. Patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma, solitary plasmacytoma, and plasma cell leukemia were also excluded. Patients with primary amyloidosis (AL) were included only if features of multiple myeloma predominated.

Initial values were derived from laboratory tests performed within 1 month of the diagnosis of multiple myeloma. Laboratory test results, radiographs, and other test results obtained more than 30 days before or after the diagnosis of multiple myeloma were recorded as missing and not reported. Distributions of the results for each laboratory test were obtained to determine the frequency and distribution of any laboratory value. Any value that did not appear compatible was reassessed.

Follow-up letters were written to all patients and to each patient's physician when the patient had not been seen or heard from during the previous year. If necessary, letters were written to other contacts of the patient, such as hospitals or other medical institutions where the patient had been. Death certificates were requested when needed. Patients granted authorization for reporting in accordance with the Mayo Foundation Institutional Review Board and Minnesota state law.

RESULTS

Criteria for the diagnosis of multiple myeloma were fulfilled for 1027 patients seen at the Mayo Clinic in Rochester, Minn, from January 1, 1985, through December 31, 1998. Two percent of patients were younger than 40 years, and 38% were 70 years or older (Table 1); the median age was 66 years. Of these 1027 patients, 59% were men, 97% were white, and 1% were African American, a reflection of the ethnic composition of Mayo Clinic patients.

History

Bone pain was present at diagnosis in 58% of patients: mild in 29%, moderate in 20%, and severe (grade 3 or 4) in 9%. The pain persisted for 6 months or less in 73% of patients and for 12 months or less in 91% before the diagnosis of multiple myeloma. The pain was often severe and usually precipitated by movement. Fatigue was usually related to anemia and was recorded as a major symptom in 32% of patients; the duration of fatigue was 6 months or less in 90% and 12 months or less in 96% before the diagnosis of multiple myeloma. The median hemoglobin value was 9.9 g/dL in patients with fatigue and 11.1 g/dL in

Table 1. **Demographic Data for 1027 Patients With Multiple Myeloma**

Factor	% of patients
Age (y)	
<40	2
40-49	8
50-59	20
60-69	32
70-79	28
≥80	10
Median	66
Range	20-92
Sex	
Male	59
Female	41
Race	
White	97
African American	1
Other	2

those without fatigue. Weight loss occurred in 24% of patients, 50% of whom had a weight loss of 9 kg or more. Paresthesias were recorded in 5%. Fever due to multiple myeloma occurred in 0.7% of patients and correlated well with disease activity. The Eastern Cooperative Oncology Group Performance Status was 0 in 38%, 1 in 37%, and 3 or 4 in 10% of patients.

Almost half of the patients had a family history of malignancy. A family history of cancer in first-degree relatives was found in 42% of patients, hematologic malignancy (excluding plasma cell disorders) in 6%, and multiple myeloma in 2%. Among the 16 patients with a family history of multiple myeloma, the disorder occurred in siblings of 11 patients, parents of 6, and a child in 1. In 2 of the 16 patients, a mother and sister both had multiple myeloma.

A personal history of another nonhematologic malignancy was reported in 19 patients at the time of diagnosis of myeloma. In addition, 7 patients had a non–plasma-cell hematologic malignancy: lymphoma in 3, chronic lymphocytic leukemia in 2, acute leukemia in 1, and a lymphoproliferative disorder in 1.

Before the diagnosis of multiple myeloma, 210 patients had had an MGUS recognized, 96 a smoldering, indolent, or evolving myeloma, 52 a solitary plasmacytoma, and 10 AL. Thus, more than a third of patients had a plasma cell proliferative process recognized before the diagnosis of multiple myeloma (Table 2).

To provide the median survival of patients with de novo presentation of multiple myeloma (no prior history of a plasma cell proliferative disorder) compared with the median survival in patients with a prior history of a plasma cell disorder, one must correct for age and sex. Patients with a recognized MGUS are older on average than those without MGUS. This is a consequence of age bias in ordering serum protein electrophoresis and of the fact that MGUS is detected incidentally and not because of symptoms or physical findings. There is also an imbalance with respect to sex. Consequently, it is necessary to adjust for age and sex in the survival curves when patients who have a prior detection of MGUS are compared with those who do not have a recognized prior MGUS. This analysis was done with a Cox model to estimate the common age and sex survival effect across all patients. Curves were then plotted for a standard reference patient from each group (male, age

Table 2. **Plasma Cell Disorders Recognized Before the Diagnosis of Multiple Myeloma***

Disorder	No. (%) of patients	Duration before diagnosis of myeloma (mo)		Median survival† (mo)	
		Median	Range	With‡	Without§
MGUS	210 (20)	81	2-340	34	36
SMM	96 (9)	23	2-300	53	34
Solitary plasmacytoma of bone	48 (5)	18	1-134	61	35
Extramedullary plasmacytoma	4 (0.4)				
Primary amyloidosis	10 (1)	3	1-151	6	37
Total	368// (36)				
Any prior plasma cell disorder	350 (34)	50	1-340	41	33

*MGUS = monoclonal gammopathy of undetermined significance; SMM = smoldering multiple myeloma.
†Age and sex adjusted to a common reference patient (65-year-old male).
‡Patients with a prior history of a plasma cell proliferative disorder.
§Patients without a prior history of a plasma cell proliferative disorder.
//Eighteen patients had more than 1 disorder before the diagnosis of multiple myeloma (eg, MGUS followed by SMM).

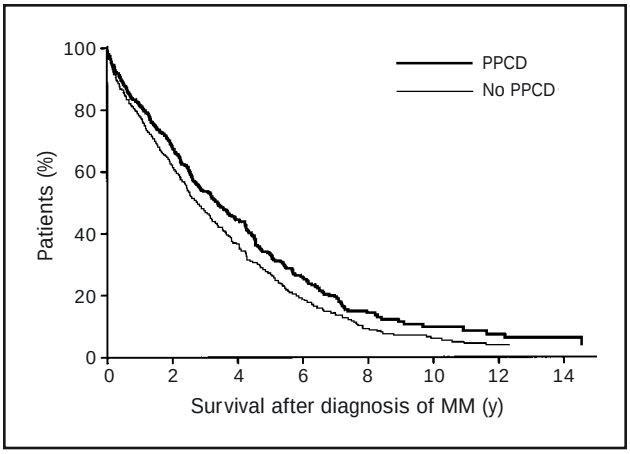

Figure 1. Duration of survival after diagnosis of multiple myeloma (MM) in patients with and without a prior plasma cell disorder (PPCD). (Standard reference patient, male, 65 years old.) *P*=.009.

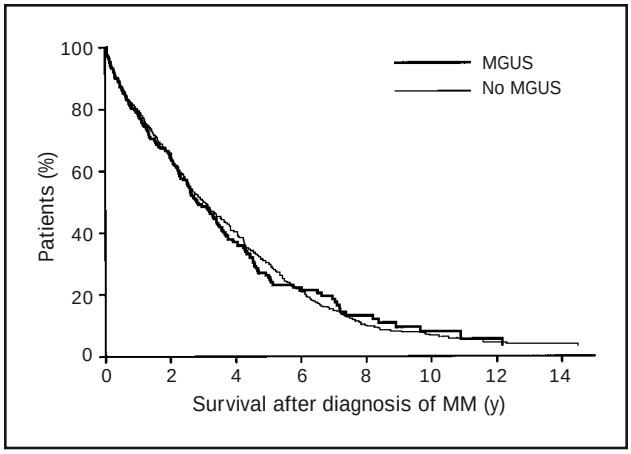

Figure 2. Median duration of survival after diagnosis of multiple myeloma (MM) in patients with and without monoclonal gammopathy of undetermined significance (MGUS). (Standard reference patient, male, 65 years old.) *P*=.75.

65 years). The age-adjusted survival was 39 months in patients with a prior plasma cell disorder and 31 months in those presenting de novo (Figure 1). There was no difference in survival in those with or without a preceding MGUS (Figure 2). Survival from diagnosis of myeloma was significantly longer in patients with prior recognition of smoldering multiple myeloma or solitary plasmacytoma, but the reverse was found in patients with AL (Table 2). The longer survival was apparently due to close surveillance and earlier diagnosis of multiple myeloma.

Physical Examination

The liver was palpable in 4% of the patients, and the spleen was palpable in 1%. Lymphadenopathy was noted in 1% of patients (Table 3).

Laboratory Tests

Hematologic Factors.—Anemia (hemoglobin concentration ≤12 g/dL) was present initially in 73% of patients (Table 4). It was generally moderate in severity; only 7% of patients had a hemoglobin value of 8 g/dL or less. The anemia was usually normocytic and normochromic, but the mean corpuscular volume was more than 100 fL in 9% of patients. Six of 53 tested patients with a mean corpuscular volume greater than 100 fL had a vitamin B_{12} level lower than 200 ng/L, 1 other patient had a serum folate value lower than 3.5 μg/L, and 2 of 10 tested patients had a positive Coombs test. One percent of patients had a mean corpuscular volume lower than 80 fL; 3 of 10 tested patients had a low serum iron value. The Coombs test was positive in 21 of 75 patients tested, of whom 19 had a hemoglobin value lower than 12 g/dL. The hemoglobin value was more than 12 g/dL in 27% of patients. Of the 193 patients who had the hemoglobin value redetermined, 168 had a value of 12 g/dL or lower. Thus, 97% of patients evaluated had a hemoglobin value of 12 g/dL or lower during the course of their disease.

Table 3. **Organomegaly in Patients With Multiple Myeloma**

	Not palpable (%)	1-3 cm (%)	4-5 cm (%)	>5 cm (%)
Liver	96	2	0.5	1.5
Spleen	99	1	0.2	0.1
Lymph nodes	99	1	0.0	0.0

Typically, the erythrocyte sedimentation rate is increased in patients with multiple myeloma. The rate was more than 20 mm/h in 84% of our patients and more than 100 mm/h in a third.

The initial leukocyte count was 4×10^9/L or lower in 20% of patients and lower than 2×10^9/L in 1%. Leukocytosis (leukocyte count $>10 \times 10^9$/L) was found initially in 8% of patients; 8 patients had leukocytosis with a count of more than 25×10^9/L. This was associated with chronic lymphocytic leukemia (2 patients), acute myelocytic leukemia (1), myeloproliferative disorder (1), and leukemoid reaction (3). Plasma cell leukemia was subsequently recognized in 1 patient who initially was thought to have hairy cell leukemia. The leukemoid reaction was due to an episode of acute renal failure in 2 patients, and the third patient had an indeterminate febrile illness. In 4 patients, the absolute lymphocyte count was 15×10^9/L or greater; 3 of these patients had chronic lymphocytic leukemia, and 1 had hairy cell leukemia that subsequently was recognized as plasma cell leukemia. The differential count showed

Table 4. **Laboratory Test Results in 1027 Patients With Multiple Myeloma**

	No. of patients	Results		Distribution of results	% of patients
		Median	Range		
Hemoglobin (g/dL)	1025	10.9	2.7-17.2	≤8	7
				8.1-10.0	28
				10.1-12	37
				>12	28
Creatinine (mg/dL)	1020	1.2	0.5-18.2	<1.3	52
				1.3-1.9	29
				≥2	19
Calcium (mg/dL)	1018	9.6	7.0-17.2	≤10.1	72
				10.2-10.9	15
				≥11	13
Cholesterol (mg/dL)	364	173	52-433	≤100	10
				>250	9
Triglyceride (mg/dL)	332	124	25-640	≤100	33
				>250	12
β_2-Microglobulin	735	3.9	0.8-82	≤2.7	25
				2.8-4.0	28
				4.1-6.0	21
				>6	26
C-reactive protein	285	0.4	0.01-49	<0.8	66
				>5.0	10

plasma cells in 3% of patients. Increased rouleau formation was present in 56% of patients. Thrombocytopenia (platelet count $<100 \times 10^9$/L) was present initially in 5% of patients. The platelet count was lower than 30×10^9/L in 3 patients: 2 had idiopathic thrombocytopenic purpura, and 1 had sepsis. Thrombocytosis (platelet count $\geq 500 \times 10^9$/L) was present in 2% of patients.

The serum calcium, creatinine, cholesterol, triglyceride, β_2-microglobulin, and C-reactive protein values are listed in Table 4. The creatinine value was more than 8 mg/dL at diagnosis in 13 patients. Five patients with an initial creatinine value lower than 5 mg/dL responded to therapy, but dialysis was required in the remainder. The serum uric acid value was more than 8.0 mg/dL in 27% of patients and more than 12 mg/dL in 2%. The serum alkaline phosphatase value was more than 300 U/L in 9% of patients and more than 500 U/L in 2% (reference ranges, 98-251 U/L and 119-309 U/L for men and women, respectively). Only 2 patients had an alkaline phosphatase value greater than 1000 U/L: 1 had AL, and 1 had undefined liver disease. The aspartate aminotransferase value was more than 100 U/L in 8 patients, 2 of whom had AL. The total serum bilirubin value was increased in 8 patients: AL was proved or suspected in 3, chronic liver disease occurred in 3, and no apparent cause was found in the remaining 2 patients.

The prothrombin time was increased (>12 seconds) in 37% of the 370 patients tested. The serum carotene value was less than 48 μg/dL in 8 of the 35 patients in whom it was determined; none had a documented malabsorption syndrome. The serum lactate dehydrogenase value was 260 U/L or more in 7% of the 165 patients in whom it was determined.

The serum viscosity was increased in 76% of the 91 patients in whom it was determined; it was 4 cP or more in 7%. The true frequency of hyperviscosity is likely much less because patients selected for viscosity measurement were those with high serum M-protein values or those who had symptoms suggestive of the hyperviscosity syndrome.

Serum and Urine Proteins.—Serum electrophoresis revealed a localized band on cellulose acetate or agarose gel or a sharp peak on the densitometer tracing in 82% of patients (Table 5). The band migrated in the γ range in 54%, in the β range in 13%, between β and γ in 12%, and in the α_2 range in 1%. Two spikes (biclonal) were found in 2% of patients. Hypogammaglobulinemia (<0.7 g/dL) was

Table 5. **Results of Serum and Urine Protein Electrophoresis***

Mobility of spike	% of patients	
	Serum	Urine
γ	54	20
β-γ	12	0
β	13	12
α_2	1	1
Hypogammaglobulinemia	8	0
Biclonal	2	0
Albumin and small globulin spike	0	60
Mainly albumin	0	4
Normal	11	3

*Total does not equal 100% because of rounding.

Table 6. **Types of Serum Monoclonal Proteins in 1027 Patients With Multiple Myeloma***

Type	% of patients
IgG κ	34
IgG λ	18
IgA κ	13
IgA λ	8
IgM κ	0.3
IgM λ	0.2
IgD κ	1
IgD λ	1
Free κ only	9
Free λ only	7
Biclonal	2
Negative	7

*Total does not equal 100% because of rounding.

found in 8% of patients, and the pattern was normal appearing in 11%. In the patients with hypogammaglobulinemia or a normal pattern, 94% had an abnormality in the urinary protein electrophoretic pattern. This consisted of only albumin in 12%, α-globulin spike in 36%, β-globulin spike in 23%, and γ-globulin spike in 23%. The median size of the M-protein spike in the 151 patients with a measurable globulin spike in the urine was 1.0 g/24 h.

Immunoelectrophoresis or immunofixation of the serum was performed in all 1027 patients. An M-protein was detected in 93% (Table 6). Sixteen percent had only a κ or λ serum M-protein (Bence Jones proteinemia); 63% had a κ M-protein, and 37% had a λ M-protein. The concentration of the serum M-protein was lower than 1.0 g/dL in 18% of patients and was lower than 3 g/dL in 43% (Table 7). One or more uninvolved immunoglobulins were reduced in 91% of patients, and both were reduced in 73%. The uninvolved immunoglobulins were reduced in 97% of patients with an IgA M-protein; both immunoglobulins were reduced in 87%. The uninvolved immunoglobulins were reduced in 88% of patients with an IgG M-protein; both uninvolved immunoglobulins were decreased in 67%. Thus, 12% of patients with IgG myeloma maintained both normal IgA and IgM levels at diagnosis.

The serum albumin value was lower than 3 g/dL in 15%. Of the 5 patients with a value lower than 2 g/dL, 4 had AL. Cryoglobulinemia was detected in 2% of the 643 patients tested.

Electrophoresis of urine was performed in 957 patients. The densitometer pattern showed a small albumin and a small globulin spike in 60%. A γ spike was found in 20%, β spike in 12%, and α_2-globulin in 1%. Four percent had only an albumin spike, and 3% had normal results (Table 5). Thirteen patients had nephrotic syndrome. This was due to AL (7 patients), diabetes (2), light-chain deposition disease (2), glomerulosclerosis (1), and an indeterminate cause (1).

Immunoelectrophoresis or immunofixation revealed a κ M-protein in 49% of patients and a λ monoclonal light chain in 29%; the remaining 22% had no monoclonal light chain. Of the patients with a monoclonal light chain, 63% had κ and 37% had λ. Immunofixation of the urine was not done in 9 patients. In 2 patients, the monoclonal light chain was found in the serum but not in the urine.

The urinary M-protein value ranged from 0.2 or lower to 14.7 g/24 h in 721 patients (Table 8). Two thirds had an M-protein value of 1.0 g/24 h or lower.

Nonsecretory Myeloma.—Three percent of patients had no M-protein in the serum and urine on immunofixation at the diagnosis of myeloma. During follow-up, an M-protein developed in the serum in 5 patients (2 with monoclonal heavy chain and 3 with monoclonal light chain). In 2 others, a monoclonal light chain developed only in the urine. Thus, in 22 of the 29 patients (76%), the condition remained nonsecretory throughout follow-up. In 1 of the 7 patients with a serum M-protein, a small IgG κ M-protein and subsequently a small IgG λ M-protein developed after autologous stem cell transplantation. The 2 M-proteins probably represented posttransplantation recovery. In 3 patients, a κ M-protein developed, and the other 3 had a λ M-protein. The uninvolved immunoglobulins were reduced in 92% (Table 9). None of the patients with nonsecretory myeloma had a serum creatinine value greater than 2 mg/dL (Table 10). The median duration of

Table 7. **Concentration of Serum Monoclonal Protein in Patients With Multiple Myeloma (N=884)**

Monoclonal protein (g/dL)	% of patients
≤0.5	15
0.6-0.9	3
1.0-1.9	11
2.0-2.9	14
3.0-3.9	22
4.0-4.9	16
≥5	19

Table 8. **Concentration of Urine Monoclonal Protein in Patients With Multiple Myeloma (N=721)**

Monoclonal protein (g/24 h)	% of patients
≤0.2	36
0.21-0.5	15
0.51-1.0	15
1.1-2.0	12
2.1-3.0	7
3.1-5.0	8
>5.0	7
Median	0.48
Range	≤0.2 to 14.7

Table 9. **Nonsecretory and Light-Chain Myeloma: Uninvolved Immunoglobulins**

	No. of patients	Uninvolved immunoglobulin (%)			
		↓1	↓2	↓3	None
Light-chain	206	15	20	52	13
Nonsecretory	29	32	16	44	8

survival was 38 months for patients with nonsecretory myeloma (Figure 3) and 33.4 months for the entire cohort of 1027 patients (P=.60).

Light-Chain Myeloma.—Two hundred six patients had only a light chain in the serum or urine. Thirty-eight patients had a monoclonal light chain in the serum. The uninvolved immunoglobulins were reduced in 87% (Table 9). The serum creatinine value was 2 mg/dL or more in 35% of patients with light-chain myeloma (Table 10). A measurable M-protein spike in the urinary protein electrophoretic pattern was found in 190 patients. The median value of the M-protein spike was 1.3 g/24 h; 38% had a 24-hour urinary M-protein value of 2 g or more. Sixty percent were κ and 40% were λ. Immunofixation of the urine was not performed at diagnosis in 11 patients, but 5 had positive results when immunofixation was done later; immunofixation was not done in 4 patients, but all 4 had a monoclonal light chain in the serum; 1 patient had a biclonal light chain (κ and λ); and in 1 patient immunofixation of the urine was negative, but the serum was positive for a monoclonal light chain. The median duration of survival of patients with light-chain myeloma was 34 months (Figure 4), which did not differ from the 33 months in the cohort of 1027.

Table 10. **Nonsecretory and Light-Chain Myeloma**

	Creatinine ≥2.0 mg/dL (% of patients)	Median survival (mo)
Light-chain	35	34
Nonsecretory	0	38

Radiographic Studies.—Conventional radiographs revealed an abnormality in 79% of patients at the time of diagnosis. Lytic lesions were found in about 67% of patients, and approximately 20% each had osteoporosis, pathologic fractures, or compression fractures of the spine (Table 11). In 25% of the 208 patients without radiographic abnormalities at the time of diagnosis, lytic lesions, pathologic fractures, compression fractures, or osteopenia developed subsequently during follow-up. Thus, in 84% of patients, skeletal lesions developed at some point during the course of their disease. The percentage would have been higher if the patients had been studied repeatedly throughout the course of their disease.

Bone Marrow Examination.—The bone marrow contained 10% or more plasma cells in 96% of patients (Table 12). The plasma cells were measured by differential count of the aspirate, estimating the number of plasma cells in the aspirate, determining the percentage of plasma cells in the plasma cell labeling index specimen, and estimating the plasma cells in the biopsy specimen. The maximal level for any determination was taken as the plasma cell content.[9] The median value of plasma cells was 50%. Forty-two patients had less than 10% bone marrow plasma cells, but lytic lesions were present in 83%. The serum M-protein value was more than 3 g/dL in 17%, the M-protein value in urine was more than 1 g/24 h

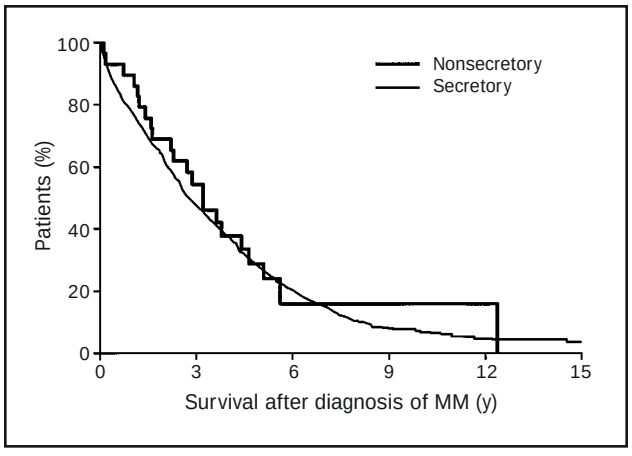

Figure 3. Duration of survival in patients with nonsecretory myeloma and those with secretory myeloma after diagnosis of multiple myeloma (MM).

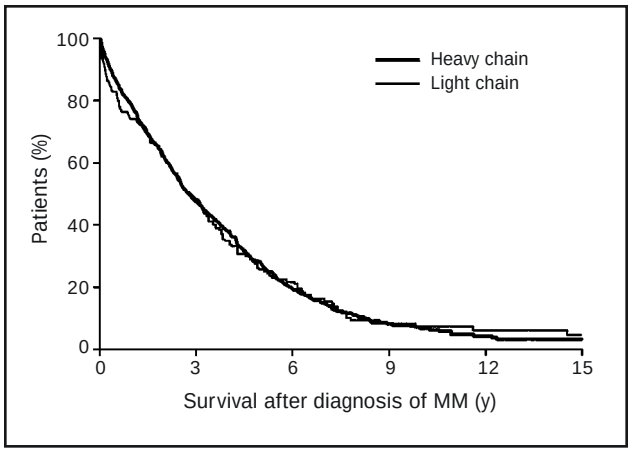

Figure 4. Duration of survival in patients with light-chain myeloma and those with heavy-chain myeloma after diagnosis of multiple myeloma (MM).

Table 11. **Radiographic Findings in Patients With Multiple Myeloma (N=1005)**

Finding	% of patients*
Lytic lesions	66
Pathologic fractures	26
Compression fracture	22
Osteoporosis	23
Osteosclerosis	0.5
Negative	21

*Total is more than 100% because many patients had more than 1 abnormality.

in 17%, and the hemoglobin value was 12 g/dL or lower in 38%.

The bone marrow plasma cell labeling index was determined in 945 patients (Table 13). The determination was technically impossible in the remaining 82 patients because of an inadequate number of plasma cells. The plasma cell labeling index was 1% or more in 34% of patients. Circulating plasma cells of the same isotype were found in 73% of patients (Table 14).

Plasma cell leukemia (plasma cells $>2000 \times 10^9$/L) occurred in 15 patients during the course of multiple myeloma. Primary amyloidosis was recognized in 10 patients before the diagnosis of multiple myeloma and in 30 patients within 30 days of the diagnosis of myeloma. In 20 patients, AL occurred during the course of the multiple myeloma. Thus, 6% of the patients with multiple myeloma had AL.

Treatment

Treatment consisted of melphalan and prednisone in 56% of patients, and a combination of alkylating agents was given to 17% (Table 15). Autologous stem cell transplantation was performed in 10% of patients.

In 15 patients, acute myelocytic leukemia (6 patients) or myelodysplastic syndrome (9 patients) developed after chemotherapy. Cytogenetic abnormalities were found in all 9 patients who were tested. Monosomy of chromosome 5 or chromosome 7 was present in 8 patients, and a complex karyotype was found in 1. Chemotherapy consisted of alkylating agents in all patients. The duration from onset of therapy to the development of myelodysplastic syndrome was 46 months and for the development of acute leukemia, 50 months. The median survival after diagnosis was 2 months.

Table 12. **Bone Marrow Plasma Cells in Patients With Multiple Myeloma (N=1027)**

Plasma cells (%)	% of patients
<10	4
10-20	13
21-30	13
31-40	11
41-50	13
51-60	12
61-70	10
71-80	11
>80	13
Median	50
Range	1-100

Survival

The median overall duration of survival was 33 months. The median duration of survival of the patients after the diagnosis compared with the expected survival is shown in Figure 5. The duration of survival was 40.5 months for patients younger than 70 years and 26.4 months for those 70 years or older ($P<.001$) (Figure 6). The median duration of survival did not differ among patients according to the year of diagnosis: 1985-1987, 1988-1990, 1991-1994, and 1995-1998 ($P=.78$) (Figure 7). The median survival of patients treated with oral melphalan plus prednisone chemotherapy was 31 months (577 patients). The corresponding median survival for patients treated with all other regimens was 38 months (450 patients).

Prognostic Findings

The following factors were evaluated for their effect on survival: age, sex, hemoglobin, platelet, calcium, and creatinine values, performance status, serum albumin value, presence of serum IgG, IgA, or light chain only, concentration of serum M-protein, presence of κ or λ urinary light chains, concentration of urine M-protein, percentage of bone marrow plasma cells, and bone marrow plasma cell labeling index (Table 16). In addition, β_2-microglobulin, determined in 735 patients, was analyzed by computational evaluation. Lactate dehydrogenase was not included in the analysis because data were available for only 16% of the patients. Furthermore, only 10% of patients had an increase in the lactate dehydrogenase value. Similarly, C-reactive protein was not included because it was measured in only 28% of patients. Detailed results of the univariate analysis, including hazard ratios and survival differences, are summarized in Table 16.

Multivariate analysis revealed that age, plasma cell labeling index, platelet count, serum albumin value, and the log of the creatinine value were the most important prognostic factors. Because the plasma cell labeling index is often not determined in practice, the multivariate analysis was repeated without this factor. Age, low platelet count, serum albumin value, and log of the creatinine value were still important prognostic factors.

DISCUSSION

The age and sex distributions of the 1027 patients were similar to those of the 869 patients with multiple myeloma

Table 13. **Bone Marrow Plasma Cell Labeling Index in Patients With Multiple Myeloma (N=945)**

Labeling index (%)	% of patients
0	25
0.1-0.5	26
0.6-0.9	15
1.0-2.0	21
2.1-3.0	7
>3	6
Median	0.5
Range	0-30

Table 14. **Peripheral Blood Plasma Cells in Patients With Multiple Myeloma**

Peripheral blood plasma cells (absolute $\times 10^6$/L)	% of patients
0	27
1-2.9	22
3-9.9	18
10-99.9	22
≥100	11

seen at the Mayo Clinic from 1960 to 1971[6] with respect to the median age and percentage of patients younger than 40 years. Only 1% were African American, but this rate is similar to the ethnic composition of Mayo Clinic patients. However, in the current study, 38% of patients were 70 years or older, compared with 23% in the earlier study. The incidence of multiple myeloma is much higher in the elderly population, and the higher percentage of patients 70 years or older in the current series is probably due to an aging population. In addition, more older patients are able to travel to a tertiary center because of better transportation, greater education, and more awareness of the disease and the need to obtain a second opinion. In the current study, only 2% of patients were younger than 40 years at diagnosis. In our experience, this percentage has not changed since we developed our database for multiple myeloma in 1960 (N=4831). In the Iowa Surveillance, Epidemiology, and End-Results Registry,[10] 40 (1%) of the 4041 patients with multiple myeloma from 1973 to 1998 were younger than 40 years.

The most common presenting symptoms in the current study were bone pain (58%) and fatigue (32%). Interestingly, weight loss, which is not a commonly recognized feature of myeloma, was reported by 24% of patients, half of whom had lost 9 kg or more. As expected,[11] unexplained fever was a rare presenting symptom, noted in less than 1% of patients. However, fever is common in patients with preterminal myeloma characterized by dedifferentiation of plasma cells and extramedullary disease.[12]

Almost half of the patients in this series had a family history of cancer in first-degree relatives. Multiple myeloma was reported in a first-degree family member in 2% of patients. Grosbois et al[13] described 15 families with 2 or more first-degree relatives with multiple myeloma. There appears to be a genetic element in some patients. We are reviewing our experience with familial multiple myeloma.

As expected, anemia was a major manifestation of myeloma and was present initially in 73% of patients. The mechanism in most patients is inadequate production of red blood cells due to either erythropoietin deficiency from accompanying renal failure or pronounced marrow replacement by myeloma cells. In some patients, anemia is disproportionate to renal failure or marrow involvement and is thought to be related to cytokine-mediated marrow suppression.[14,15] Another mechanism may involve shortened red blood cell survival; however, overt immune hemolytic anemia is rare, and a positive Coombs test was noted in only 2% of patients in the current study.

The serum creatinine level was increased in almost half of our patients, and one fifth had a serum creatinine value of 2.0 mg/dL or more at the time of diagnosis. The major causes of renal failure are myeloma kidney (precipitation of monoclonal light chains in distal and collecting tubules) and hypercalcemia. Other causes include dehydration, hyperuricemia, and AL.

The serum protein electrophoretic pattern showed a spike or localized band in 82% of patients. The remainder had hypogammaglobulinemia or a normal-appearing pattern. An IgG M-protein was found in more than half of the patients, and an IgA M-protein was found in about 20%. The serum contained a free monoclonal light chain in 16% of patients. Only 2% of patients had a biclonal gammopathy. IgD myeloma is uncommon and was found in only 2% of patients. The size of the serum M-protein spike is usually more than 3 g/dL, but one fifth of patients had a serum M-protein spike lower than 1 g/dL. Thus, the size of the M-protein spike is not helpful for excluding the diagnosis of multiple myeloma.

Table 15. **Initial Treatment of Multiple Myeloma in 1027 Patients***

Treatment	No. (%) of patients
Conventional-dose chemotherapy	
Melphalan + prednisone	577 (56)
Combination alkylating agents	177 (17)
VAD	70 (7)
Radiation	38 (4)
Corticosteroids	8 (1)
Other	13 (1)
Unknown	46 (4)
High-dose chemotherapy with stem cell transplantation	98 (10)

*VAD = vincristine, doxorubicin (Adriamycin), dexamethasone.

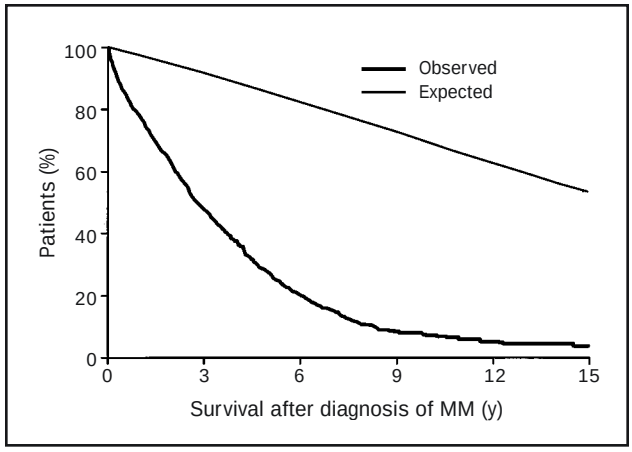

Figure 5. Duration of survival after diagnosis of multiple myeloma (MM) in 1027 patients and expected survival. Median of observed and expected survival, 2.8 years and 16.6 years, respectively.

Reduction of uninvolved immunoglobulins is common. A monoclonal light chain is found in the urine in almost 80% of patients. An M-protein was found in the serum or urine or both in 97% of our patients with multiple myeloma at the time of diagnosis. Three percent of the patients had no M-protein in the serum or urine and were designated as having nonsecretory myeloma. Renal insufficiency was uncommon in this group of patients. Only one fourth of our patients with nonsecretory disease had development of secretory disease during follow-up. Survival, however, was not different than that in the patients with secretory myeloma. In other series, the survival of patients with nonsecretory myeloma was similar to that in patients with an M-protein.[16,17] Dreicer and Alexanian[18] reported a median survival of 39 months in patients with nonsecretory myeloma, which is almost identical to that in our patients. Twenty percent of our patients had light-chain myeloma. Although a serum creatinine value of 2 mg/dL or more was more common than in the large cohort, the survival was virtually identical.

Conventional radiographs showed abnormalities consisting of punched-out lytic lesions, osteoporosis, or fractures in 79% of our patients at the time of diagnosis. Osteosclerotic lesions were rare.[19,20] Technetium 99m bone scanning is inferior to conventional radiography and should not be used. Large lytic lesions may be overlooked on radionuclide scans because osteoblastic activity does not occur. Computed tomography is helpful in patients who have bone pain but no abnormalities on radiography.[21] Abnormal magnetic resonance imaging patterns were obtained in 82% of 61 patients with multiple myeloma in one study.[22] Magnetic resonance imaging of spinal cord compression is useful for diagnosis.[23] The bone marrow contained 10% or more plasma cells in 96% of patients in the current study. The plasma cell labeling index may be helpful for confirming the diagnosis of multiple myeloma. A monoclonal antibody (BU-1) reactive with 5-bromo-2-deoxyuridine identifies the plasma cells that synthesize DNA. The BU-1 does not require denaturation, and therefore fluorescent conjugated immunoglobulin antisera (κ and λ) identify monoclonal plasma cells and plasmacytoid lymphocytes.[24] The plasma cell labeling index was 1% or more in 34% of our patients. However, 25% of patients with active multiple myeloma requiring therapy had a labeling index of 0%, and more than half had a labeling index of 0.5% or less.

Several important prognostic factors were identified in our study (Table 16). Most of these also have been identi-

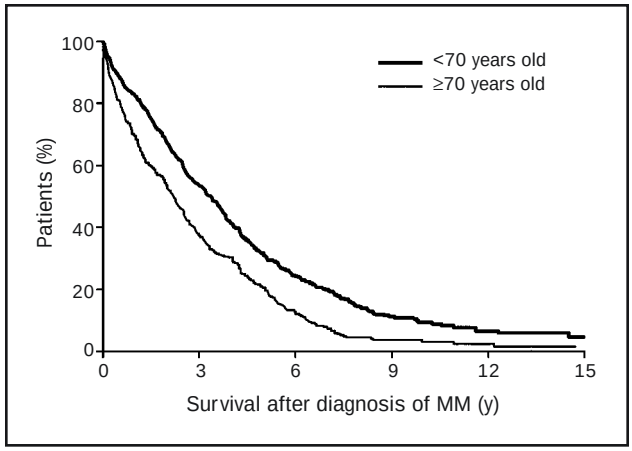

Figure 6. Duration of survival of patients after diagnosis of multiple myeloma (MM), according to age of patients.

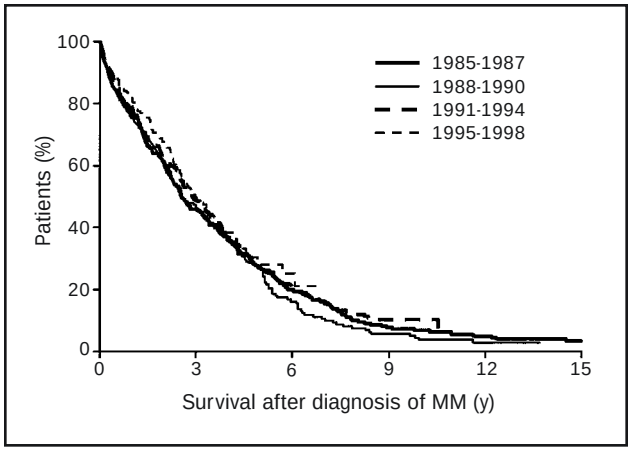

Figure 7. Duration of survival of patients after diagnosis of multiple myeloma (MM) did not differ according to year of diagnosis.

Table 16. **Univariate Analysis of Prognostic Factors for Survival in Multiple Myeloma***

Prognostic factor	Median survival in presence vs absence of adverse prognostic factor (mo)	Overall survival	
		Relative risk (95% CI)	*P* value
Age ≥70 y	26 vs 41	1.5 (1.3-1.8)	<.001
Performance status 3 or 4	11 vs 36	1.9 (1.6-2.4)	<.001
Hemoglobin ≥10 g/dL	27 vs 38	1.3 (1.2-1.5)	<.001
Platelet count <150,000 × 10^9/L	24 vs 37	1.5 (1.2-1.8)	<.001
Serum calcium ≥11	23 vs 35	1.3 (1.1-1.6)	.006
Serum creatinine ≥2	21 vs 36	1.5 (1.3-1.8)	<.001
Serum albumin ≥3	18 vs 37	1.7 (1.4-2.0)	<.001
β_2-Microglobulin >4 mg/L	28 vs 40	1.5 (1.3-1.8)	<.001
Plasma cell labeling index ≥1%	25 vs 40	1.5 (1.3-1.7)	<.001
Bone marrow plasma cell percentage ≥50%	31 vs 38	1.2 (1.0-1.4)	.01

*CI = confidence interval.

fied as markers of high-risk disease in other studies; thus, they are reliable and well-validated tools for counseling and patient care decisions. Many of the prognostic factors identified are simple clinical or laboratory variables such as age, performance status, platelet count, and hemoglobin, serum albumin, serum calcium, and serum creatinine values, all of which can be easily determined in all patients. Other factors such as β_2-microglobulin level and the bone marrow plasma cell labeling index have been repeatedly shown to have independent prognostic value in myeloma.[25,26] Although not analyzed in the current study, we and others have shown that the presence of plasmablastic features,[27] deletion of chromosome 13,[28,29] high lactate dehydrogenase level,[30] and circulating plasma cells[31] are other important adverse prognostic factors in myeloma. The use of powerful, independent prognostic factors in myeloma has overcome the limitations of the Durie-Salmon staging system[32] that has been used for almost 3 decades as a staging and prognostic system for multiple myeloma.[26]

As shown in Table 16, the presence of a single adverse prognostic factor results in lowering of median survival by several months. An important issue is which single factor or combination of factors provides the best prognostic information for patient care. We believe that a risk-based staging system that uses a combination of independent prognostic factors provides greater prognostic information than any prognostic factor alone.[26] For newly diagnosed disease treated with standard-dose chemotherapy, 2 recently described models are valuable. One model (the "Mayo stage") described by Greipp et al[33] uses β_2-microglobulin value and bone marrow plasma cell labeling index. The median survival for patients with 0, 1, or 2 abnormal factors was significantly different at 71, 58, and 34 months, respectively. This system was later validated by the Eastern Cooperative Oncology Group.[34] The second model, described by investigators from the Southwest Oncology Group, uses the combination of β_2-microglobulin and serum albumin values (SWOG stage).[35] For patients undergoing stem cell transplantation, Desikan et al[8] developed a staging system that uses the combination of β_2-microglobulin level, deletion of chromosome 13 on karyotype analysis, C-reactive protein value, and prior chemotherapy more than 12 months before transplantation. The overall survival was 5 months for patients in whom all the factors were abnormal and 62 months for those in whom all 4 factors were favorable.

When prognostic factors are combined into a risk-based staging system, it is important to remember that most prognostic factors are interrelated and that choosing the best combination can be complicated. First, although several combinations (including those listed previously) have been suggested, most have limitations.[26] For example, some prognostic factors (such as plasma cell labeling index) used in these systems cannot be assessed readily at all centers and some are time-consuming to obtain. Second, none of the systems is universally accepted, and thus use is limited. An International Prognostic Index for myeloma that uses a combination of well-validated but simple and readily available factors is being developed by a panel of leading myeloma researchers from around the world (P.R.G., personal communication).

The overall survival in this series was 33 months compared with 20 months in the series of 869 patients seen at the Mayo Clinic from 1960 to 1971. Other studies report much better survival, but they represent highly selected cohorts of patients undergoing one or more autologous stem cell transplantations for myeloma.[7,8] Stem cell trans-

plantation improves survival in myeloma, but it is not an option for many elderly patients (>70 years of age), for patients with serious comorbid conditions, and for patients with poor performance status.[36] In the current study, only 98 patients received autologous stem cell transplantation because most were treated before evidence showed the superiority of stem cell transplantation.[37] Moreover, this study represents a cohort of all patients with myeloma seen over a 14-year period rather than a selected group of patients eligible for stem cell transplantation. Bladé et al[38] showed that patients who are candidates for stem cell transplantation have a better prognosis than patients who are ineligible for the procedure because of increased age, performance status, or other factors.

During the course of the current study, survival did not improve from 1985 through 1998. Alexanian and Dimopoulos[39] showed that there was no improvement in survival from 1965 to 1991. Although disappointing, these results are expected because none of the standard-dose chemotherapeutic regimens studied during the past 3 decades show survival benefit over the oral regimen of melphalan plus prednisone.[40] However, there is much reason to believe that survival has improved significantly in the past 5 years for patients with myeloma. First, as previously discussed, the use of stem cell transplantation has been shown to prolong survival significantly compared with standard-dose chemotherapy.[37] Second, the agent thalidomide has recently shown significant activity in relapsed myeloma, with a median response duration of approximately 1 year.[41] Third, promising new agents such as bortezomib (Velcade, PS-341)[42] and CC5013 (an immunomodulatory analogue of thalidomide)[43,44] have shown impressive activity in patients with advanced myeloma. Finally, improvements in supportive care for patients with bony lesions[45] and efforts to develop oral maintenance regimens[46] are ongoing. These advances, coupled with remarkable strides in the understanding of the biology of the disease,[47,48] provide considerable hope and optimism for both patients and myeloma researchers.

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