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Clinical Staging and Therapeutic Results in Multiple Myeloma

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Abstract—*The validity of the Durie and Salmon's clinical staging system for multiple myeloma has been tested in* 81 *consecutive patients studied at the Istituto Nazionale Tumori of Milan from January* 1970 *to June* 1982. *Median survival from diagnosis was* 48 months *for stage I,* 41 months *for stage II and* 23 months *for stage III* ($P = 0.02$). *Median survival of patients with normal renal function (A) was* 35 months *and of those with abnormal kidney function (B)* 7 months. *Almost all early deaths were observed in patients with stage III disease associated with renal failure. No statistically significant difference was found in the median survival in patients with κ and those with λ light chains. The analysis of survival according to the three main combinations of chemotherapy used in this study (melphalan–prednisone vs melphalan–procarbazine–prednisone vs adriamycin–prednisone) could not disclose any significant difference. Prognosis was, however, closely related to the response to combination chemotherapy: median survival was* 72 months *in responders,* 36 months *in patients with improvement and* 25 months *in non-responders* ($P < 0.01$). *A lower incidence of response was obtained in patients with stage III myeloma compared to patients with stage I–II. The myeloma staging system used in this study is simple to employ and allows identification of truly comparable patient groups in the evaluation of therapeutic results. Our therapeutic results confirm the effectiveness of melphalan plus prednisone and fail to demonstrate any advantage in the administration of adriamycin as first-line therapy.*

INTRODUCTION

MULTIPLE myeloma has served as a model of neoplastic disease both in experimental animals and in man. Studies in the mouse clearly showed the quantitative correlation between the serum myeloma protein (M-component) concentration and tumor weight [1] and provided the experimental basis for calculating myeloma cell mass in patients with IgG myeloma from measurements of rates of monoclonal immunoglobulin synthesis and metabolism [2]. Several reports have investigated factors which influence prognosis in multiple myeloma. The main parameters which have been identified include the performance status, the M-component type and subtype, the presence or absence of renal failure, the hemoglobin level, the extent of bone lesions, the bone marrow histology, the serum concentration of albumin and calcium and other less important features [3–17]. In 1975 Durie and Salmon [4], by correlating the presenting clinical features, response to treatment and survival with the measured myeloma cell burden, developed a clinical staging system for multiple myeloma. Several reports supported that this clinical staging system was closely correlated to the prognosis of multiple myeloma [6, 8–11, 14].

The purpose of this report is to retrospectively analyze the survival of patients with multiple myeloma according to either Durie and Salmon's clinical staging system or treatment administered.

MATERIALS AND METHODS

This report contains an analysis of 81 consecutive patients with multiple myeloma followed at the Istituto Nazionale Tumori of Milan from January 1970 to June 1982.

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Criteria for diagnosis

The diagnosis of multiple myeloma required at least two of the following: (1) increased plasma cell counts in bone marrow or other tissues; (2) a rise in levels of M-component in the serum and/or urine during observation; (3) typical radiological bone lesions [18].

Initial evaluation

The initial evaluation included measurement of blood hemoglobin, leukocytes and platelets, marrow aspiration (frequently associated with bone marrow biopsy), quantitative serum electrophoresis, 24-hr urine protein with electrophoresis of a concentrated sample, immunoelectrophoresis of the serum or urinary M-component, serum calcium, serum creatinine, blood urea nitrogen (BUN), uric acid, chest X-ray and a complete skeletal survey.

Clinical staging

Patients were divided into three stages according to the clinical staging (Table 1) described by Durie and Salmon [4]. The degree of bone lesion was evaluated as described by Merlini *et al.* [8]: normal bones, 0; osteoporosis or solitary lytic lesion, 1; multiple lytic bone lesions and/or multiple compression fractures, 2; destruction of more than one skeletal segment and/or major fractures, 3.

Characteristics of patients

The main patient characteristics are reported in Table 2. Sixty-one patients (75.5%) had multiple myeloma, 13 (16%) Bence Jones myeloma and 7 (8.5%) non-secreting myeloma. The median age was 60.5 yr (range, 38–77 yr), with a similar distribution in both sexes (males, 40; females, 41). Seventeen patients received elsewhere their first treatment, consisting of radiotherapy in 3 cases and chemotherapy with single agent +/- radiotherapy in the others. Eleven patients (14%) were classified as stage I (A, 11; B, 0), 15 (18.5%) as stage II (A, 14; B, 1) and 55 (68%) as stage III (A, 48; B, 7). Median duration of follow-up was 32 months (range, 1–142 months).

Treatment modalities

In this series all patients regardless of their clinical staging were treated with anticancer chemotherapy. The first-line therapy consisted of: (1) melphalan 6 mg/m^2 p.o. for 4 days plus prednisone 100 mg/m^2 p.o. for 4 days in 40 patients. The cycle was restarted on day 29; (2) the same plus procarbazine 100 mg/m^2 p.o. for 10 days in 14 cases. The cycle was restarted on day 43;

*Table 1. Myeloma staging system**

Stage	Criteria	Measured myeloma cell mass (cells × 10^{12}/m^2)†
I	All of the following:	
	hemoglobin value >10 g/100 ml	
	serum calcium value ≤12 mg/100 ml	
	on X-ray, normal bone structure or solitary bone plasmocytoma only	<0.6
	low M-component production rates	(low)
	IgG value <5 g/100 ml	
	IgA value <3 g/100 ml	
	urine light chain M-component on electrophoresis <4 g/24 hr	
II	Fitting neither stage I nor stage III	0.6–1.20 (intermediate)
III	One or more of the following:	
	hemoglobin value <8.5 g/100 ml	
	serum calcium value >12 mg/100 ml	
	advanced lytic bone lesions	
	high M-component production rates	
	IgG value >7 g/100 ml	
	IgA value >5 g/100 ml	>1.20
	urine >12 g/24 hr	(high)

Subclassification

A: relatively normal renal function (serum creatinine value <2.0 mg/100 ml)‡

B: abnormal renal function (serum creatinine value ≥2.0 mg/100 ml)

*See Durie and Salmon [4].

†10^{12} cells: approximately 1 kg.

‡If the serum creatinine is not available, the blood urea nitrogen (BUN) value may be used as an indicator of renal function. (A BUN value of 30 mg/100 ml is roughly equal to a serum creatinine value of 2 mg/100 ml).

Table 2. Characteristics of patients

Total cases	81
multiple myeloma	61 (75.5%)
Bence Jones myeloma	13 (16.0%)
non-secreting myeloma	7 (8.5%)
Median age (yr)	60.5 (range 38–77)
Sex (M/F)	40/41
Prior therapy*	17 (RT: 3; CT ± RT: 14)
Stage:	
I	11 (13.5%)
II	15 (18.5%)
III	55 (68%)
A	73 (90%)
B	8 (10%)
Median follow-up (months)	32 (range 1–142)

*RT: radiotherapy; CT: chemotherapy.

(3) adriamycin 45 mg/m² i.v. on day 1 plus prednisone 100 mg/m² p.o. for 4 days in 18 patients. The cycles were repeated each 3 weeks. In 9 cases other combinations were employed: cyclophosphamide alone or in combination with vincristine, adriamycin and prednisone was given in 3 cases; vincristine, adriamycin, BCNU and prednisone alternated monthly with vincristine, melphalan, cyclophosphamide and prednisone in two cases. Four patients received radiotherapy alone. Radiotherapy was utilized combined with chemotherapy for the treatment of painful osteolytic lesions (31 cases) and spinal cord compression (4 cases). All patients received additional supportive therapy as required.

According to the criteria of response developed by the Southwest Oncology Group [19], patients were judged to be responsive to treatment when a decrease of pathologic parameters was observed of 75% or more on at least two measurements at a 4-week interval.

Patients with less than 75% decrease in serum M-protein in the absence of progression were considered to be 'improved'. Those who failed to satisfy the criteria for the responsive or improved categories were classified as failures. Patients who died within 3 months from start of therapy were considered as early deaths.

Statistical analysis

Survival curves were calculated from the date of diagnosis for the different prognostic parameters. They were computed using the Kaplan–Meier product limit method. Statistical tests were carried out by use of the log-rank test. Survival was studied as a function of initial stage, type of M-component, treatment schedule and response to therapy.

RESULTS

By June 1982, 15 of the 81 patients included in the present series were alive, 65 were dead and 1 was lost to follow-up after 7 months from diagnosis. Death could be related to multiple myeloma in 37 patients, to renal failure in 13 cases, to sepsis in 4 patients and to hemorrhage in 3 instances. In 5 patients death was apparently unrelated to multiple myeloma (cardiovascular accident), and in 3 cases the cause of death remained unknown. The overall median survival was 32 months, with 9.6% of cases surviving at 8 yr. Median survival was 48 months for stage I patients, whereas the median survival of patients classified as stages II and III was 41 and 23 months respectively (Fig. 1). The difference was significant at $P = 0.02$. According to the subclassification in A and B, the median survival was 35 and 7 months respectively (Fig. 2), but no statistical significance was detected. When survival rates were related to

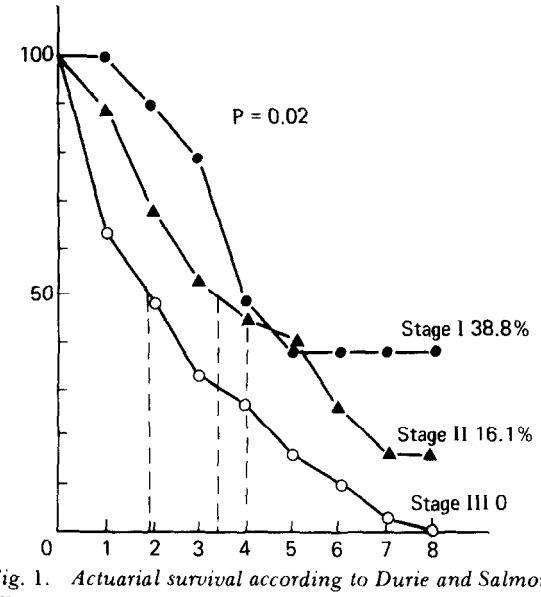

Fig. 1. Actuarial survival according to Durie and Salmon's clinical staging system. Stage I vs II, P = 0.37; *stage I vs III,* P = 0.02; *stage II vs III,* P < 0.05.

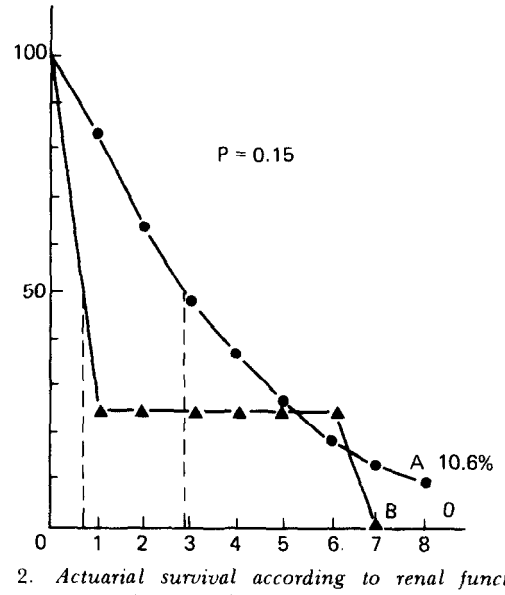

Fig. 2. Actuarial survival according to renal function (A = normal; B = abnormal).

the type of M-component (IgG, IgA, Bence Jones, non-secreting) no significant difference was found. Nevertheless a better prognosis was observed in patients with IgG myeloma compared to patients with IgA myeloma ($P = 0.07$).

No difference ($P = 0.63$) was found in the median survival with regard to the type of light chain produced (κ, 43 months; λ, 24 months). In Table 3 is reported the therapeutic response related to the 3 major types of therapy administered. Eleven of 72 patients were not evaluated as they received their first chemotherapy elsewhere. Of the 61 evaluable patients 33 were given melphalan and prednisone, 12 melphalan, procarbazine and prednisone and 16 adriamycin and prednisone respectively. The pretreatment characteristics of the three groups were similar, particularly with regard to stage. The incidence of response $\geqslant 75\%$ was 31%, with no significant differences related to the type of therapy administered. No major differences were observed with regard to the initial stage either (Table 4). However, a lower incidence of response $\geqslant 75\%$ was obtained in patients with stage III myeloma compared to patients with stage I–II. It is noteworthy that almost all early deaths were observed in patients with advanced stage III disease, especially when associated with renal failure (B subgroup).

No significant difference was found in the survival related to the type of treatment administered (Fig. 3). However, therapeutic response was closely related to prognosis (Fig. 4). The median survival was in fact significantly better among responders (72 months) than among patients with improvement (36 months) and non-responders (25 months), with $P < 0.01$.

DISCUSSION

Tumor staging has achieved widespread acceptance as a prerequisite for the optimal planning and analysis of chemotherapy programmes for many types of cancer. In myeloma a number of features correlating with a bad prognosis have been defined [3–16]. However, whilst these prognostic factors were useful in predicting outcome in individual cases, they could not be incorporated into a sufficiently comprehensive or accurate classification suitable for use in prospective trials of therapy. The clinical staging system introduced in 1975 by Durie and Salmon has the advantage of incorporating all of the relevant prognostic factors as well as of being based on the quantitative assessment of tumor cell mass [4]. Several retrospective (Table 5) as well as prospective [7] analyses have confirmed the validity of this staging system. This report

Table 3. Therapeutic response related to the type of chemotherapy in previously untreated patients

Chemotherapy	Evaluable patients	Early death	Type of response (%) Failure	Improvement	Response $\geqslant 75\%$
Melphalan + prednisone	33	12	27	33	28
Melphalan + procarbazine + prednisone	12	8	17	42	33
Adriamycin + prednisone	16	—	37.5	25	37.5
Total	61	8	28	33	31

Table 4. Therapeutic response related to stage

Stage	No. of cases	Early death	Type of response (%) Failure	Improvement	Response $\geqslant 75\%$
I	11	—	18	45.5	36.5
II	13	—	23	23	54
III	37	13.5	32.5	32.5	21.5
A	55	3.5	31.5	32.5	32.5
B	6	50	—	33.5	16.5

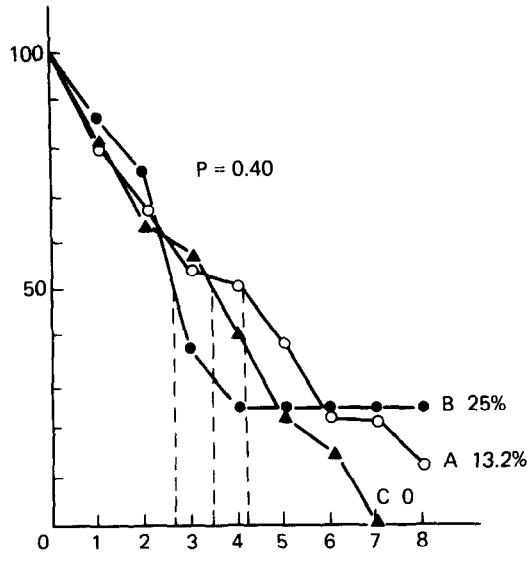

Fig. 3. Actuarial survival according to the type of treatment. A = Melphalan + prednisone; B = melphalan + prednisone + procarbazine; C = adriamycin + prednisone.

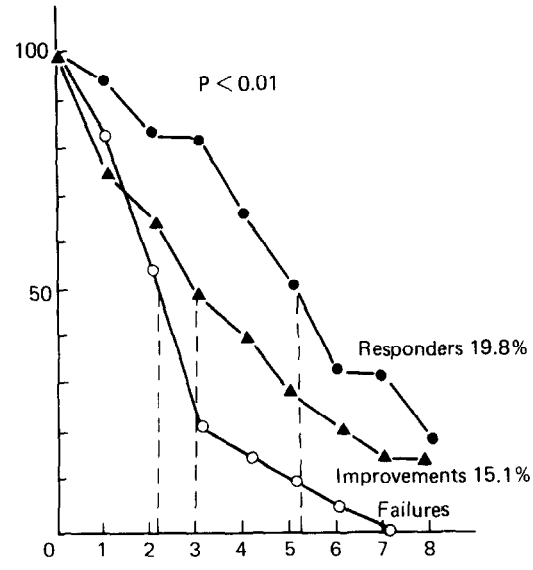

Fig. 4. Actuarial survival according to the type of therapeutic response. Responders vs improvements, P = 0.18; responders vs failures, P < 0.01; improvements vs failures, P = 0.14.

confirms these results and demonstrates significant differences in survival among patients with the different tumor cell mass stages. Although not statistically significant, the importance of renal impairment is again demonstrated in this study, suggesting a prompt and energetic therapy to prevent and treat renal failure. The myeloma staging system proposed by Durie and Salmon is simple to employ and allows identification of truly comparable patient groups in the evaluation of therapeutic results as a basis for planning new prospective randomized trials.

Although the staging system of Durie and Salmon does not incorporate tumor response, for which a predictive test is not available, this represents an important prognostic factor significantly influencing survival, as confirmed in our series. Another myeloma staging system, based on standardized graphs given the presenting serum creatinine and calcium and the percentage of plasma cells on bone marrow examination, has recently been published [8]. However, this system has not yet been tried by other investigators. Nevertheless, the inclusion of the degree of bone marrow plasmacytosis makes its widespread use dubious.

The median survival of patients with multiple myeloma in the era before the introduction of alkylating agents has been estimated at 17 months from the time of the first symptoms and 7 months from the time of initial treatment [20]. Major improvements in the treatment of myeloma patients began with the introduction of melphalan. However, irrespective of whether this alkylating drug is administered alone or in combination with prednisone, or whether it is given continuously or intermittently at low or high dose regimens, little progress has been recorded in myeloma treatment [16].

A number of trials with combination chemotherapy have been conducted to improve the response rate and survival compared to patients treated with melphalan and prednisone. The majority of these trials showed no benefit, and no induction therapy has been shown to be superior to intermittent melphalan and prednisone in a prospective randomized study [17–21].

The results of two studies [22, 23] have shown

Table 5. Median duration of survival according to stage at diagnosis

Series	No. of cases	Median survival (months) Stage: I	II	III	A	B
Durie and Salmon [4]	71	>60	50	26	—	—
Alexanian *et al.* [6]	343	39	27	17	—	—
Woodruff *et al.* [14]	237	64	32	6	21	2
Merlini *et al.* [8]	123	76	41	12	—	—
Belpomme *et al.* [9]	118	>60	28	7	>60	12
Gobbi *et al.* [11]	91	>79	51	33	—	—
Present series	81	48	41	23	35	7

the effectiveness of adriamycin in alkylating-resistant patients, suggesting the use of this drug as a first-line treatment of multiple myeloma. Our therapeutic results with three combinations confirm that the effectiveness of melphalan and prednisone is comparable to the other two regimens and fail to demonstrate any advantage in the administration of adriamycin as first-line therapy. The poor remission rate obtained in stage III myeloma strongly suggests the establishment of more effective chemotherapy combinations by utilizing our knowledge on cellular kinetics of multiple myeloma [24]. From this point of view the results of the vincristine-containing regimens given at 3-week intervals in the SWOG trials [25] and of the M-2 protocol from the Memorial Sloan-Kettering Institute [26], which showed apparently significantly higher remission rates and longer median survival when compared to melphalan and prednisone, are noteworthy, but require randomized comparisons.

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