PROGNOSTIC FACTORS IN MULTIPLE MYELOMA

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The effect of certain disease parameters on remission and survival time was evaluated in 482 patients with multiple myeloma treated with intermittent courses of melphalan–prednisone combinations. Increasing degrees of anemia, hypercalcemia, azotemia, and high serum myeloma protein levels were associated with progressive lifespan shortening. The short survival of patients with anemia and hypercalcemia was associated with short remissions in responding patients with these abnormalities. The extent of tumor mass was defined from specific laboratory parameters reported by Durie[12] to be associated with large numbers of plasma cells. More advanced stages of myeloma were associated with higher frequencies and degrees of normal immunoglobulin depression. The response rate was not affected by the tumor mass grade, but increasing tumor mass was associated with a shorter lifespan. Greater degrees of tumor reduction were associated with longer remission and survival times. Patients in whom a marked tumor reduction was rapid had shorter survival and remission times than patients who responded more slowly.

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MULTIPLE MYELOMA IS A MALIGNANCY OF plasma cells with many disease manifestations. Since the availability of effective chemotherapy with alkylating agents, either alone or in combination with corticosteroids, the survival time of patients with this disease has lengthened significantly.[2,6,11] Certain harmful disease features, such as hypercalcemia and renal failure, have been recognized for many years;[9,11,16] yet, very few quantitative evaluations of these prognostic factors have ever been conducted in patients receiving combination chemotherapy. Correlations of prognostic factors with the degree and duration of remission have never been evaluated. This study assessed the relationship between certain patient characteristics and the response rate, the frequency, degree and duration of remission, and the survival time of patients with multiple myeloma treated with combinations of melphalan and prednisone. The myeloma tumor mass was also assessed in each patient from criteria defined by Durie and Salmon.[12] The frequency of a response to chemotherapy was similar regardless of the initial tumor load. Longer remissions and survival times occurred in patients with a lower plasma cell number and more marked degrees of tumor reduction.

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METHODS

This report contains an analysis of 482 patients with multiple myeloma registered consecutively between September, 1965 and December, 1972 by seven Southwest Oncology Group (SWOG) institutions on a series of treatment programs with melphalan and prednisone. Only symptomatic patients without prior chemotherapy with alkylating agents were eligible for treatment and analysis. The diagnosis required bone marrow plasmacytosis exceeding 10%, in association with a monoclonal globulin peak on serum or

urine electrophoresis. Sixteen patients without monoclonal proteins were also included when other typical abnormalities were present; these patients were considered not evaluable for analyses of remission but evaluable for studies of survival time. In 440 patients, the antigenic type of heavy and/or light chains of the monoclonal protein was identified by immunoelectrophoresis.

All patients received combination chemotherapy with intermittent courses of melphalan and prednisone, either with or without added vincristine and/or procarbazine, in accordance with specific SWOG treatment protocols. Details of the dose regimens employed have been presented elsewhere.[2,4,5] In essence, 132 patients received intermittent courses of melphalan and prednisone; 226 received melphalan, prednisone, and procarbazine; and 124 received a four-drug combination with vincristine added in a dose of 1 mg intravenously every 10–20 days. The response rate, survival, remission duration, and the frequency of major disease complications were identical for all treatment groups;[5] all patients were combined in this analysis of prognostic factors and remission kinetics.

Clinical response was determined no sooner than 4 weeks from the start of treatment; patients who died within 4 weeks were considered "early deaths." When a response occurred, treatment was continued indefinitely through the remission period until relapse or death. The only exceptions were 65 responsive patients who were allocated to receive either no treatment or BCNU–prednisone after at least 12 months of melphalan–prednisone therapy; these patients were included in this analysis of prognostic factors only after remission duration and survival were found to be identical to that for patients receiving indefinite melphalan treatment.[5] Clinical response was evaluated from criteria previously defined in detail and based on marked, sustained declines in myeloma protein production rate to less than 25% of the pretreatment value.[4,19] The known variations in the catabolic rate of IgG myeloma proteins with changing serum concentration were considered in calculating the frequency, degree, and duration of remission.[21] Survival curves were determined from the institution of chemotherapy to death for all patients, including "early deaths," patients with inadequate records, and patients who died of diseases considered unrelated to myeloma.[14] At the time of this analysis, 80% of the patients were dead. The remission duration of responding patients was calculated from the duration of sustained decline in myeloma protein production below 25% of the pretreatment value.

The influence of a variety of clinical parameters documented before the institution of chemotherapy was evaluated on: 1) frequency of early death, 2) response rate, 3) degree of remission, 4) remission duration, and 5) survival time. These parameters included age, sex, race, hemoglobin concentration, blood urea nitrogen (BUN), serum calcium, and myeloma protein levels. The tumor mass was estimated for each patient from criteria defined from direct measurements of plasma cell number in other myeloma patients studied by Durie and Salmon.[12] The effects of tumor mass grade before treatment and the degree of tumor reduction after treatment were correlated with prognosis.

RESULTS

Age, Sex, and Race

Only one positive correlation was found between the age, sex, and race of myeloma patients and the survival and remission parameters evaluated in this study (Table 1). The median survival time of patients older than 65 years (20 months) was shorter than that of patients less than 55 (26 months) ($p < .05$). There was no association between the age, sex, or race and a specific myeloma protein type. All other differences with respect to age, sex, and race were not significant (Table 1).

Hemoglobin

Patients with severe anemia (i.e. hemoglobin less than 8.5 g/100 ml) prior to chemotherapy had a shorter median survival time (15 months) than other patients with more mild degrees of anemia. Median survival times were significantly longer with serial elevations in hemoglobin value (Table 1, Fig. 1). The remission duration of responding patients was also shorter with increasing degrees of anemia (Table 1). Thus, a short remission duration was a major factor contributing to the short survival time of patients with severe anemia.

Hypercalcemia

Of the patients in this series, 22% had a corrected serum calcium level greater than 11.5 mg/100 ml before treatment (Table 1). The serum calcium concentration was cor-

TABLE 1. Effect of Certain Disease Parameters on Survival and Remission in Multiple Myeloma

Clinical features	No. patients (%)	No. early deaths (%)	Median survival (mo)	Response rate (% evaluable)	Median remission duration (mo)
TOTAL	482 (100)	21 (4)	23	57	20
Age					
<55	130 (27)	3 (2)	26	59	17
55–65	190 (39)	10 (5)	24 *	53	24
>65	162 (34)	8 (5)	20	59	18
Sex					
Male	276 (57)	13 (5)	22	58	18
Female	206 (43)	8 (4)	24	56	21
Race					
White	389 (81)	17 (4)	24	58	20
Black	93 (19)	4 (4)	22	51	17
Hemoglobin (g/100 ml)					
<8.5	136 (28)	11 (8)	15 *	45 *	11 * †
8.5–10.5	156 (32)	7 (4) †	24 †	61 *	18 †
>10.5	190 (40)	3 (2)	31 *	62	26
Corrected calcium (mg/100 ml)					
>12.5	67 (14)	5 (7)	11 *	59	11 * †
11.5–12.5	38 (8)	2 (5)	19 †	63	19
<11.5	371 (78)	14 (4)	26	57	23
BUN (mg/100 ml)					
>40	88 (18)	11 (13) †	13 †	55	15
<40	388 (82)	10 (3)	25	57	20

* p = .01–05.
† p = <.01.

rected for the serum albumin level in order to present a more valid index of the ionized calcium value. This was justified in myeloma patients because of their wide variations in serum albumin concentration, the principal protein in blood that binds calcium. The formula (corrected calcium (mg/100 ml) = serum calcium (mg/100 ml) − serum albumin (g/100 ml) + 4.0) was used to calculate the "corrected serum calcium" for each patient.[17] An increased serum calcium level was not associated with either a significantly higher frequency of "early deaths" during the first 4 weeks of treatment or a lower response rate (Table 1). However, there was a marked shortening of remission duration and lifespan (Table 1, Fig. 1). Hypercalcemic patients with a blood urea nitrogen (BUN) value less than 40 mg/100 ml showed the same degree of life shortening as other hypercalcemic patients with more severe azotemia. Thus, as in patients with severe anemia, a short remission duration for responding patients contributed to the short survival of patients with hypercalcemia.

Blood Urea Nitrogen (BUN)

Of the patients in this series, 18% had a BUN greater than 40 mg/100 ml (Table 1). Patients with a BUN greater than 40 mg/100 ml had a higher frequency of early death and a shorter median survival time than did patients with lower BUN values (Table 1, Fig. 1). The median survival for 41 patients with a BUN between 30–40 mg/100 ml (24 months) was similar to that for patients with a BUN less than 30 mg/100 ml (25 months). The response rate and remission duration in patients with an elevated BUN was not significantly different from that found in patients with normal renal function (Table 1, Fig. 1).

The frequency of azotemia was evaluated in myeloma patients with different protein types (bottom of Table 2). About one-fourth of the patients with IgA peaks or only Bence Jones proteins had BUN values greater than 40 mg/100 ml prior to treatment. The frequency of irreversible azotemia (i.e. BUN persisting above 30 mg/100 ml) was highest in myeloma patients producing only Bence Jones protein; most of these patients had a level of proteinuria that exceeded 1.0 g/day.

Combinations of Abnormalities

When two or more of the detrimental disease features described above occurred in combination, the effect on prognosis was not worsened. Only 10 patients (4% of total) had

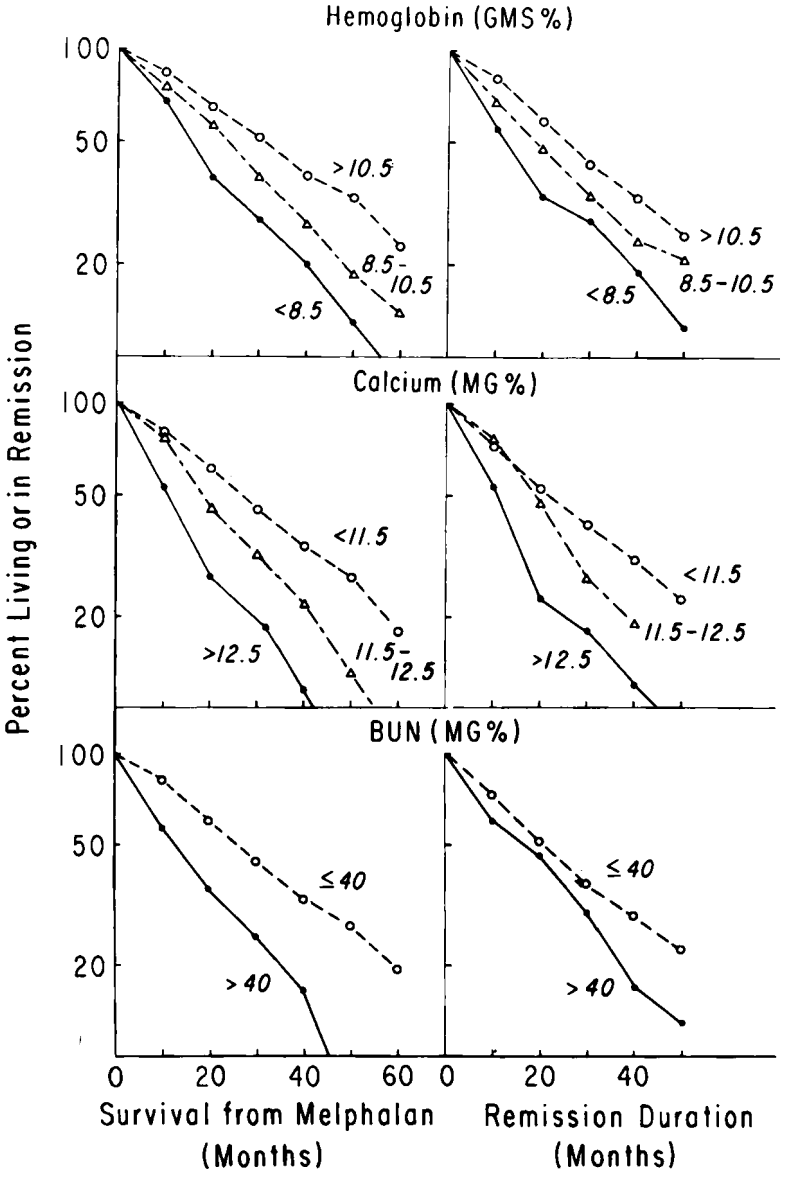

FIG. 1. Survival and remission duration curves for groups of patients with different degrees of anemia, hypercalcemia, and azotemia. Patients with the most severe abnormalities are indicated by closed circles, those with intermediate values by triangles, and those with near normal levels by open circles.

a triple combination of these degrees of severe anemia, hypercalcemia, and azotemia.

Myeloma Protein and Serum Albumin Level

The level of myeloma proteins before treatment was correlated with prognosis. Patients with markedly elevated serum myeloma proteins (IgG peak > 7.0 g/100 ml or IgA peak > 5.0 g/100 ml) usually had shorter survival times and shorter remission durations than patients with lower protein values (Table 3). Most of the differences found were not significant ($p > .05$). No correlation was noted between prognosis and the amount of Bence Jones protein excretion before treatment. Low levels for serum albumin concentration (< 3.0 g/100 ml) were also associated with a short survival time and remission duration (Table 3); hypoalbuminemia was associated with the previously described complications with a higher frequency than normal serum albumin levels.

Protein Type

The effect of myeloma globulin type on prognosis was evaluated. Patients with IgA peaks had a similar response rate, but a shorter median survival and remission duration, in comparison with patients with IgG peaks (Table 3). The short survival time was asso-

TABLE 2. Frequency of Abnormalities in Patients with Different Myeloma Protein Types

	Protein types*			
	IgG	IgA	K only	L only
No. patients	254	106	42	38
Median age (years)	62	61	62	59
Sex (% males)	54	62	61	66
Race (% black)	20	19	24	13
Anemia (% hemoglobin <8.5 g/100 ml)	26	39	22	29
Hypercalcemia (% corrected calcium >11.5 mg/100 ml)	17	35	27	16
% Depressed normal immunoglobulins†	50	58	36	45
% High tumor mass	36	56	31	24
Azotemia (% BUN > 40 mg/100 ml)	13	25	29	26
Irreversible azotemia‡	5	14	20	26
% Bence Jones proteinuria (% >1.0 g/day)	21	26	91	100

* Percent of each type unless indicated.

† Includes only MDAH, Ohio State, Scott and White patients with two or more of the following: IgM < 30 mg/100 ml, IgA < 50 mg/100 ml, and IgG < 500 mg/100 ml.

‡ % BUN greater than 40 mg/100 ml, remaining above 30 mg/100 ml after 2 weeks of therapy.

ciated with and attributed to the higher frequency and severity of specific disease complications (i.e. anemia, hypercalcemia, and azotemia) in patients with IgA peaks (Table 2). The survival of patients with only Bence Jones protein was similar, and the remission duration was longer, in comparison to that found in patients with IgG peaks (Table 3). The longer remission time was attributed to the more rapid disappearance of Bence Jones proteins during remission, and the presumably later reappearance during clinical relapse, in comparison with myeloma heavy chains.[1] The survival and remission duration of patients with only lambda light chains were longer than that of patients with only kappa light chains, but the differences were not significant ($p > 0.1$).

Tumor Mass

The pretreatment tumor mass of each patient was defined from slight modifications of criteria recently shown by Durie and Salmon to have a direct relationship to plasma cell number.[12] Because data on the extent of bone lesions were not available for a large fraction of our patients, this criterion was not used in this study to define the tumor mass grade. Thus, a high tumor mass was assumed when *any* of the following was present:

1) severe anemia (hemoglobin < 8.5 g/100 ml); 2) hypercalcemia (corrected calcium > 11.5 mg/100 ml); 3) markedly elevated serum myeloma protein level (IgG peak > 7 g/100 ml; IgA peak > 5 g/100 ml).

TABLE 3. Correlations of Myeloma Protein and Albumin with Prognosis

	No. patients	Median survival (mo)	Response rate (% evaluable)	Median remission duration (mo)
Protein type				
IgG	254	25 ‡	55	20
IgA	106	17	53	14 ‡
Only Bence Jones protein (all patients)	97*	24 †	60	27 ‡
Kappa only	42	20	58	19
Lambda only	38	33	60	33
Serum peak concentration (g/100 ml)				
IgG peaks				
>7	36	15 †	39	21
5.1–7	74	23	61	13 †
≤5	144	27	56	22
IgA peaks				
>5	43	16	62	10
3.1–5	30	15	50	14
≤3	33	22	42	20
Albumin (g/100 ml)				
<3.0	81	15 ‡	61	16
3.0–3.9	242	23	53	19
≥4.0	157	27	60	24

* Includes 17 patients with untyped light chains.

† $p = .01–.05$.

‡ $p = <.01$.

Low tumor mass was defined by the presence of *all* of the following: 1) no or mild anemia (hemoglobin > 10.5 g/100 ml); 2) normocalcemia (corrected calcium < 11.5 mg/100 ml); 3) low serum myeloma protein level (IgG peak < 5 g/100 ml, IgA peak < 3 g/100 ml); 4) no patient with extensive bone lesions on skeletal radiographs could qualify for a low tumor mass.

All other patients were considered to have an "intermediate" tumor mass. For patients with only Bence Jones proteins, the tumor mass was defined primarily from the hemoglobin level, the corrected serum calcium and, in confirming a low tumor mass grade, the status of bone lesions. Tumor mass could not be defined in 12 patients in whom anemia was attributed in part to severe renal failure. All had a BUN greater than 75 mg/100 and a hemoglobin concentration less than 8.5 g/100 ml, but were without specific evidence of hypercalcemia or a very high serum peak that would have confirmed a high tumor mass. Durie and Salmon have indicated the following ranges for absolute cell number within a tumor mass range:[12] high: $> 1.2 \times 10^{12}$ cells/m^2; intermediate: $0.6–1.2 \times 10^{12}$ cells/m^2; low: $< 0.6 \times 10^{12}$ cells/m^2. Table 4 tabulates the frequency and severity of certain clinical parameters in patients assigned to the different tumor mass categories. Azotemia was not considered in the definition of tumor mass, since renal failure was considered to result primarily from the product of plasma cell tumors (i.e. Bence Jones proteins) or from metabolic complications (i.e. hypercalcemia), and not from the number of tumor cells per se. Nevertheless, patients with a high tumor mass had a much higher frequency of azotemia (Table 4). Ten of the 16 patients without evidence of a myeloma protein were considered to have a low tumor mass.

TABLE 4. Clinical Parameters with Different Pretreatment Tumor Mass

	Tumor mass*		
	High	Intermediate	Low
No. patients (% of total)	218 (45)	140 (29)	112 (23)
Age (median)	61	62	59
Sex (% males)	56	51	65
Race (% black)	24	17	15
Hemoglobin (g/100 ml)			
<8.5	57	0	0
8.5–10.5	28	66	0
>10.5	15	34	100
Corrected calcium (mg/100 ml)			
>11.5	47	0	0
BUN (mg/100 ml)			
>40	30	7	3

* Each figure shows percent of patients in each tumor mass group unless indicated.

Of all patients in this series, 45% had a high tumor mass, 29% an intermediate, 23% a low, and 3% an unknown tumor mass. The response rate was slightly higher for patients with low and intermediate tumor mass (59%), in contrast to that for patients with high tumor mass (51%) (Table 5). This difference was not significant and was attributed to the less adequate treatment trials among evaluable patients with more advanced disease due to their slightly higher frequency of death during the early treatment period (i.e. from 1–6 months). The degree of remission for patients with different tumor mass grades was also similar (Table 5).

Patients with high pretreatment tumor mass had a higher frequency of early death (8%), a shorter survival, and a shorter remission duration for responsive patients, in comparison with other patients demonstrating less extensive tumor mass (Table 5, Fig. 2). Patients presenting with low tumor mass achieved long survival times and long remission durations.

Normal Immunoglobulins

The concentration of normal immunoglobulins was evaluated before chemotherapy in three institutions with reproducible immunoglobulin assays of identical serum samples (Table 6). Depressions of normal immunoglobulins were less frequent and less marked in patients with a low tumor mass. Using the Wilcoxon test, there was no difference in the levels of all three classes of normal immunoglobulins between patients with high and intermediate tumor mass; however, normal immunoglobulins were significantly higher in patients with low tumor mass in contrast to those with a high or intermediate tumor mass ($p < .002$).

Kinetics of Remission

The maximum degree of remission from chemotherapy was calculated for all 343 patients with measurable serum peaks and evaluable treatment trials. This was calculated from changes in serum myeloma protein production rate as previously described.[4,19] With

TABLE 5. Effect of Pretreatment Tumor Mass on Response Rate, Survival, and Remission

Degree of remission (% of control for serum peaks only)	Pretreatment tumor mass High	Intermediate	Low
Effect on response rate			
No. evaluable patients	171	104	68
Percent of patients for each tumor mass			
Unresponsive			
50–100	30	18	23
25–49	19	22	25
Responsive			
10–24	22	27	15
<10	29	33	37*
TOTALS	100	100	100
Total no. evaluable patients (includes patients with only Bence Jones protein)	196	125	101
Total frequency of response	51	60	58
Effect on survival and remission†			
All patients	17	27	39
Unresponsive			
50–100	9	13	27
25–49	14	22	34
Responsive			
10–24	17 (8)	25 (9)	40 (21)
<10	33 (21)	34 (24)	46 (32)*

* All patients in this group showed disappearance of their serum peak.

† Each figure indicates median survival in months for all patients/group, with numbers in parentheses indicating median remission duration for responders.

increasing degrees of tumor mass reduction below the pretreatment level, both survival and remission duration time were prolonged (Table 5). Most differences were statistically significant ($p < .05$).

The time required to induce remission was correlated with survival and remission duration. More than 50% of responding patients were in remission within 3 months, and 77% had responded within 6 months of treatment. No patient required longer than 18 months of chemotherapy before a remission was confirmed. The remission duration and survival time were evaluated in 59 patients who responded rapidly (i.e. in 2 months or less), in 52 patients who responded with an intermediate speed (i.e. after 3 and 4 months), and in 33 patients who responded more slowly (i.e. after 5 and 6 months). Patients responding between 7 and 18 months were not considered because of their guaranteed advantage in survival. Patients who responded rapidly (i.e. within 2 months) had shorter median survival and remission durations than did patients who responded during later time periods (Table 7). Rapidly responding patients did not have a higher frequency of any harmful prognostic factor associated with a short survival. Specifically, the frequency of severe anemia, hypercalcemia, azotemia, high serum myeloma

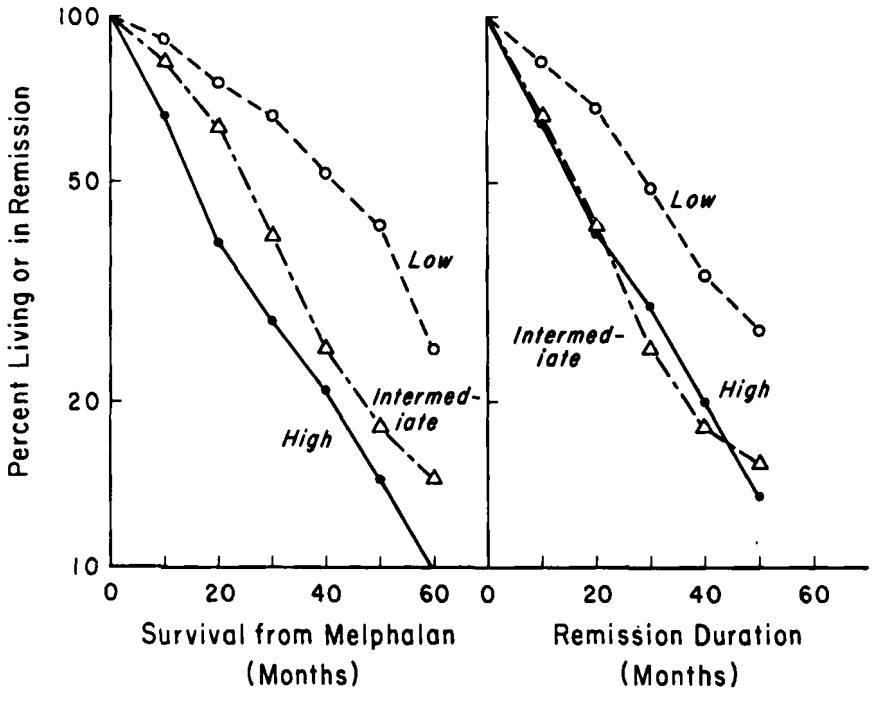

FIG. 2. Survival and remisison duration curves for groups of patients with different tumor mass grades. Patients with a high plasma cell number are indicated by closed circles, those with an intermediate number by triangles, and those with a low number by open circles.

TABLE 6. Correlation of Nonmyeloma Immunoglobulin Levels (mg/100 ml) with Pretreatment Tumor Mass

	Pretreatment tumor mass*		
	High	Intermediate	Low
No. patients†	101	64	57
IgM			
<60	95	94	70
<30	71	67	33
IgA			
<100	93	91	52
<50	69	71	26
IgG			
<1000	93	100	60
<500	62	41	23

* Each figure indicates the percentage of measurements in each tumor mass group unless indicated. In patients with IgG and IgA myeloma proteins, only two normal immunoglobulin classes were evaluated. In patients with only Bence Jones proteins, the levels of all three immunoglobulin types were assessed.

† Includes only M. D. Anderson, Ohio State, and Scott and White Clinics.

proteins, and high tumor mass grade was similar for each of the three groups. The percentage of patients achieving marked degrees of remission to less than 10% of the pretreatment value was also similar for all three groups.

DISCUSSION

Patients with multiple myeloma demonstrate marked differences in the frequency and severity of specific disease complications. This study was designed to evaluate the prognostic significance of the most common disease features. All patients included in this analysis were symptomatic and had unequivocal criteria for the diagnosis of myeloma. Only 4% of patients presented without evidence of a monoclonal peak on serum or urine electrophoresis; these patients were included only in the survival analyses. All patients were treated with intermittent courses of melphalan and prednisone at seven cooperating institutions. A large number also received vincristine and/or procarbazine in accordance with specific protocols. Since the response rate, survival, and remission duration were similar for all treatments,[5] all patients were analyzed together in this analysis of prognostic factors.

TABLE 7. Correlation of Time to Remission with Survival and Remission Time in Patients with Serum Peaks

Months to remission	No. patients	Median survival from treatment (mo)	Median remission duration (mo)
1, 2	59	18	12
3, 4	52	31 *	18 †
5, 6	33	31	20

* $p = <.05$

† $p = <.10$.

No major correlations were identified between age, sex, or race and any of the disease and response parameters evaluated in this study. These conclusions were similar to those reported by others in patients not receiving chemotherapy[9] and in patients treated with melphalan or cyclophosphamide alone.[16] The presence of severe anemia, hypercalcemia, or moderate degrees of azotemia before treatment was associated with significant survival shortening, an observation also similar to that reported by others.[9,11,16] A similar effect on prognosis was noted in patients with very high serum myeloma protein levels. The direct relationship between the magnitude of these abnormalities and the degree of lifespan shortening provided further support for the deleterious effect of these disease parameters. Since the response rates in patients with these harmful features were similar, the shortening of survival was not a result of any inherent resistance to chemotherapy. Rather, the short remission duration in responding patients with these abnormalities contributed substantially to the short survival time. Durie and Salmon have recently calculated higher numbers of plasma cells in patients with anemia, hypercalcemia, and very high serum myeloma proteins.[12] Thus, the short survival and remission times associated with these abnormalities resulted to a major degree from the larger tumor burden that produced these complications.

Renal failure was associated with a high frequency of early death and a short survival, but was not associated with any alteration in response rate or remission duration. This was consistent with the absence of any relationship between plasma cell number and azotemia,[12] and supported the contention that renal failure was unrelated to the tumor mass grade.[7] The shorter survival for patients producing IgA myeloma proteins, in contrast to those with IgG proteins, confirmed similar results in the Acute Leukemia Group B.[15] The survival and remission times were longer for patients with only lambda light chains in comparison with patients producing only kappa light chains. This observation differed from

that reported previously by the SWOG on a smaller number of patients followed for a shorter duration on a series of less effective treatment programs.[2,6] Although the differences were slight, the frequencies of hypercalcemia and high tumor mass grade were lower in patients with only lambda light chains. Most likely, the prognosis depended more on the presence of those disease complications associated with a short survival rather than on a specific myeloma protein type.

The pretreatment tumor mass was determined in each patient from laboratory criteria confirmed by Durie and Salmon to have a direct relationship to plasma cell number.[12] Thus, patients with hypercalcemia, severe anemia, or very high rates of serum myeloma protein production were considered to have more plasma cells than did patients without these features. Patients with lower tumor mass were identified when anemia was mild, hypercalcemia was absent, and serum myeloma protein production rates were not markedly elevated. Since 85% of the patients with a high tumor mass had been assigned because of severe anemia or hypercalcemia, serum myeloma protein levels were considered more useful in confirming a low tumor mass in patients without major complications. Various levels of Bence Jones protein excretion were not used in assigning a tumor mass grade since there was no clearcut relationship to absolute cell number.[12] The extent of bone lesions was also not used because documentation was not available in a large fraction of our patients. Despite some loss of precision from the failure to apply the bone lesion status to the tumor grade definition, the conclusions in regard to prognosis were considered valid. Only in the 3% of patients in whom severe renal failure may have contributed to severe anemia was it not possible to define tumor mass.

Patients with a low tumor mass showed less marked depression of normal immunoglobulins, in comparison with patients bearing larger numbers of plasma cells. Thus, the presence of normal immunoglobulin levels in a patient with few disease complications provided further evidence for a lower myeloma tumor burden. Previous studies had demonstrated that patients with localized plasmacytomas had preserved immunoglobulin concentrations,[10] and that remissions in multiple myeloma occasionally restored depressed immunoglobulin values.[3] Furthermore, surgery or radiotherapy for localized plasmacytomas has stimulated normal immunoglobulin production markedly.[10,22] These findings supported the hypothesis that the depressed production of normal immunoglobulins in myeloma was due to a chalone produced by the malignant cells whose production was reduced during remission.[19]

Patients with a high pretreatment tumor mass had similar frequencies and degrees of remission in comparison with patients showing a lower tumor burden. Thus, the proportionate magnitude of cell kill with a standard program of chemotherapy was similar for patients with different magnitudes of tumor mass load. This conclusion confirms, in a human tumor model, numerous previous observations by Skipper in rodent malignancies of a constant, fractional cell kill of cancer cells from a standard program of chemotherapy.[20] However, the remission duration achieved in responding patients with a high tumor mass was shorter than that found in responding patients with a lower tumor mass. This observation was attributed to the higher residual numbers of plasma cells remaining during "remission" in patients with high tumor mass, a conclusion again consistent with numerous studies in animal models.[20] These findings demonstrated the applicability of the laboratory criteria used to define tumor mass grade before chemotherapy and the utility of serial evaluations of myeloma protein level during treatment. Regardless of the pretreatment plasma cell population size, increasing degrees of remission were associated with longer remission and survival times. Previous studies had indicated that the prolongation in survival for responding patients with myeloma was accounted for by the remission duration.[1] Thus, these observations emphasized the need for achieving a maximal reduction in absolute cell number with chemotherapy and not merely an arbitrary percentage reduction. These conclusions about human myeloma are applicable to other disseminated human malignancies.

The determination of tumor mass grade for each patient with myeloma provided a more valid assessment of prognosis both before treatment and after different magnitudes of tumor reduction were induced by chemotherapy. Thus, as emphasized by Bergsagel,[8] prospective chemotherapy trials would become more meaningful if patients were randomized to different treatment groups in a manner which insured a similar percentage of

patients with different tumor mass levels. Since the tumor mass of a patient did not predict the likelihood of a response to chemotherapy, the utility applies primarily to analyses of survival and remission duration. Renal failure was present in only 5% of patients with a low or intermediate tumor mass; thus, a further subclassification on the basis of azotemia as proposed by Bergsagel[8] and Durie[12] is probably of little value.

About one-third of responding patients were in a remission status within 2 months of treatment; these patients had median survival and remission times about 1 year less than those responding patients who achieved remissions during subsequent months of treatment. Confirming the results of Hobbs,[13] rapidly responding patients probably had a pattern of tumor growth kinetics that was different from that of patients with slower onsets of remission. Conceivably, a higher growth fraction was present that was sensitive to chemotherapy, but resulted in the earlier relapse of a resistant cell population.

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