

Unmaintained Remissions in Multiple Myeloma

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Twenty-eight patients with multiple myeloma responding to prior melphalan-prednisone combinations, but without additional chemotherapy, were followed until relapse. Patients receiving no further treatment had a median survival time similar to that of those receiving indefinite courses of melphalan-prednisone or carmustine-prednisone. Prolonged periods of unmaintained remission occurred primarily in patients without extensive disease at the time of diagnosis or in whom the abnormal protein disappeared from

the electrophoresis strip. The initial relapse after an unmaintained remission was controlled in 80% of patients with the resumption of melphalan-prednisone, but second remissions were usually less marked in degree and shorter in duration. Results supported the long-term evaluation without chemotherapy of selected patients with low numbers of plasma cells after treatment who were likely to experience long durations of disease stability and respond again to retreatment with melphalan-prednisone.

MOST PATIENTS with multiple myeloma achieve long-term remissions of good quality with combinations of melphalan and prednisone.^{1,2} Previous studies showed that the survival time of responding patients followed without chemotherapy after the first year was similar to that of patients receiving indefinite courses of melphalan-prednisone therapy.³ This report demonstrates that part of that prolonged survival time resulted from a high frequency of second remissions after retreatment for tumor relapse. Results also indicate that the long-term followup of responding patients without chemotherapy is justified primarily when low numbers of plasma cells remain after one year of treatment.

MATERIALS AND METHODS

Twenty-eight consecutive patients with multiple myeloma were followed without chemotherapy after remissions had been achieved with melphalan-prednisone combinations administered between February 1969 and December 1972. All patients had been symptomatic, with the diagnosis based on the presence of bone marrow plasmacytosis exceeding 10%, and a monoclonal globulin peak on serum and/or urine electrophoresis. All patients had either bone destruction or decreased normal immunoglobulins; lytic bone lesions were present in 89%, and two or more normal serum immunoglobulins were markedly depressed in 79%. Those few patients without overt bone destruction also had moderate degrees of anemia (Hb < 10.5 g/dl) and/or hypercalcemia (>11.5 mg/dl).

The pretreatment tumor mass grade of each patient was defined from specific laboratory criteria based on the degree of anemia, the presence of hypercalcemia, the level of the serum myeloma protein, and the extent of lytic bone lesions; patients were assigned to a "high," "intermediate," or "low" tumor mass group as described previously.^{4,5}

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The initial treatments consisted of intermittent courses of melphalan-prednisone-procarbazine or melphalan-prednisone-procarbazine-vincristine in maximal doses.^{1,3} Clinical response was defined as a 75% reduction in serum myeloma protein production rate and the disappearance of Bence Jones protein.^{1,3} Quantitative changes in tumor mass were calculated from changes in serum myeloma protein level, the plasma volume, and the alterations in the catabolic rate of the myeloma globulin with changes in serum concentration.⁶ Only patients who were in remission after 12 mo of chemotherapy were eligible for random allocation to either continued melphalan-prednisone, carmustine (*N,N*-bis(2-chloroethyl)-*N*-nitrosourea, BCNU)-prednisone, or long-term followup without any drug treatment. The remission duration was defined as the interval between the onset of a 75% reduction in serum myeloma protein and the return to this level during relapse; in responding patients with disappearance of myeloma proteins, relapse was confirmed when an abnormal protein was again detected on an electrophoretic strip. After unequivocal disease progression was recognized, intermittent melphalan-prednisone courses were resumed and continued until death. Second remissions were confirmed when serum myeloma protein production was reduced again to a level less than 25% of the pretreatment value and to at least 40% of the maximum level reached during relapse.

RESULTS

The survival time for responding patients followed without chemotherapy until relapse was not significantly different from that of patients who received repeated courses of melphalan-prednisone or BCNU-prednisone ($p > 0.2$) (Fig. 1). The unmaintained remission duration until the first relapse was also similar for patients followed without chemotherapy (median 11 mo) compared with that for patients on either maintenance program ($p > 0.2$) (Fig. 1).

The patient groups were not precisely comparable, since patients receiving melphalan-prednisone after the first 12 mo had a higher frequency of hypercalcemia and a consequent high tumor mass grade at the time of diagnosis (Table 1). Also, a higher percentage of patients followed without treatment developed disappearance of their serum peak from their initial treatment.

Of the 28 patients assigned to followup care without any chemotherapy, as of September 1977 1 remained alive in remission, 2 died in remission of unrelated diseases, and 25 developed tumor relapse. Among these 25, 2 refused further therapy, 1 died within 4 wk, and 2 had inadequate data documentation following the resumption of melphalan-prednisone. The effects of melphalan-prednisone retreatment were evaluated in the remaining 20 patients with

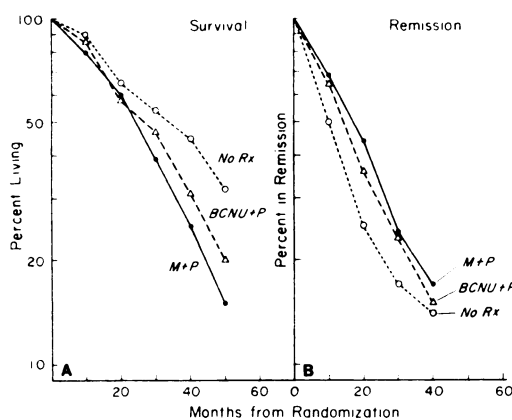


Fig. 1. (A) Survival from randomization for groups of responding patients treated with melphalan-prednisone (●), BCNU-prednisone (△), or followed without chemotherapy until relapse (○). (B) Remission duration from randomization for the same groups of patients.

Table 1. Comparability of Maintenance Treatment Groups

	Maintenance Treatments		
	No Treatment	BCNU Plus Prednisone	Melphalan Plus Prednisone
No. of patients	28	29	36
Pretreatment abnormalities (% of total)			
Hemoglobin <8.5 g/dl	18	21	17
Corrected calcium* >11.5 mg/dl	7	7	28
Blood urea nitrogen >40 mg/dl	17	17	14
Tumor mass grade (%)			
High	29	21	42
Intermediate	46	31	33
Low	25	48	25
Degree of Remission			
No. and per cent disappearance of serum peak	(9/20) 45%	(5/18) 28%	(9/25) 35%

*Corrected calcium (mg/dl) = serum calcium (mg/dl) - serum albumin (g/dl) + 4.0.

adequate posttreatment electrophoretic data. Retreatment began within 6 mo of the first evidence of rising myeloma proteins in all but 5 patients.

Of the 20 relapsing patients, 16 (80%) achieved a second remission of their disease. Figure 2 shows serial changes in tumor mass for 3 patients who had persistent serum myeloma proteins after their initial treatment and for 2 patients in whom there was disappearance of their serum monoclonal globulin. In 6 of the 8 responding patients with persistent myeloma proteins, the magnitude of reduction of the abnormal protein was less after the second program of melphalan-prednisone treatment (Fig. 2). Of 9 evaluable patients relapsing

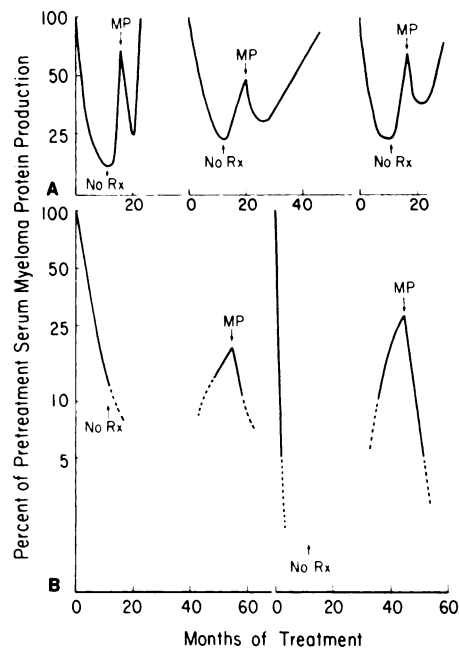


Fig. 2. Changes in tumor mass as percentage of pretreatment value during unmaintained remission (A) in three patients with residual serum peaks and (B) in two patients with disappearance of their monoclonal component. Dotted lines, assumed values when serum peak was undetectable.

Table 2. Remission Duration in Myeloma

	No. of Patients	Unmaintained Remission Duration [Median mo (range)]	Remission Durations* (mo)	
			Unmaintained†	Maintained
All patients	28	11 (1-60)		
Pretreatment tumor mass grade				
High and intermediate				
All patients	21	8 (1-46)		
Persistent serum peak	9	6 (2-12)	2	3
			3	4
			6	8
			3	8
			10	34+
Serum peak disappeared	9	14 (2-46)	26	24+
			14	18
			42	2+
Only Bence Jones protein disappeared	3	6 (1-16)		
Low				
All patients	7	27 (4-60)		
Persistent serum peak	1	20		
Serum peak disappeared	1	18	18	3
Only Bence Jones protein disappeared	5	27 (4-60)	60	8+
			4	3

*Includes only those 11 M. D. Anderson Hospital patients with two remissions.

†Excludes time in remission between onset of response and randomization (median 9 mo).

to the BCNU-prednisone maintenance program, none responded to an adequate melphalan-prednisone trial.

Specific disease features were correlated with the duration of unmaintained remission (Table 2). Long remission durations occurred most frequently in patients with a low pretreatment tumor mass (median 27 mo) or with disappearance of their serum monoclonal component regardless of the pretreatment tumor mass grade (median 16 mo). The duration of remission for 16 patients with either of these features (median 19 mo) was significantly longer than that for the remaining 12 patients with a high or intermediate tumor mass (median 6 mo) ($p < 0.01$). Of those 7 patients with an unmaintained remission duration exceeding 2 yr, there was disappearance of serum myeloma proteins in 3 and of Bence Jones proteins in 4; 4 of these patients had presented with a low tumor mass. Too few patients presented with severe anemia, hypercalcemia, or azotemia to determine the effect of each of these laboratory abnormalities on the remission duration (Table 1).

The longest unmaintained remission occurred in a patient who 20 mo after radiotherapy for a tonsil plasmacytoma developed bone marrow plasmacytosis, lytic skull lesions, and the progressive evolution of 3.5 g/day of Bence Jones proteinuria; he was considered to have multiple myeloma at a low tumor mass. There was disappearance of light chain excretion with melphalan-prednisone-procarbazine courses that were discontinued after 12 mo. All disease parameters then remained stable for 60 mo until a plasmacytoma arising from an area of bone destruction in the sternum was associated with recurrent Bence Jones proteinuria. Resumption of melphalan-prednisone was followed by reso-

lution of the mass, recalcification of the underlying lytic lesion, and the disappearance of Bence Jones protein for a second time.

For each patient, the duration of the first unmaintained remission was compared with that of the second maintained remission. When a serum peak remained as an indicator of tumor mass, the duration of the second maintained remission was similar to or longer than the duration of the initial unmaintained remission (Table 2); when the myeloma protein marker had disappeared from the serum and/or urine, the second maintained remission was similar or shorter in duration.

The rate of tumor growth during the second relapse, while the patient was receiving melphalan-prednisone, was compared with that present during the first relapse, when the patient was not receiving chemotherapy, from curves fitted to at least four measurements (Fig. 2). The data from only 5 patients were considered adequate for this comparison, and no differences were found between the tumor doubling times calculated for both relapses. When the kinetics of the first relapse were evaluated in 11 patients, 5 patients with a very rapid tumor doubling time (2 mo or less) had a median survival of 15 mo from the onset of no treatment and 3 responded to melphalan-prednisone retreatment; 8 patients with a longer doubling time (>2 mo) had a longer median survival of 45 mo and all responded to retreatment.

DISCUSSION

In patients with multiple myeloma, alterations in myeloma globulin level have provided an important index of tumor mass change after the start of chemotherapy.¹⁻⁵ In addition to defining the presence and degree of tumor reduction, serial electrophoretic studies have contributed to a more precise evaluation of the remission degree and duration as well as of the kinetics of relapse.^{4,7,8} In this study the duration of unmaintained remission and the frequency of disease recontrol were assessed in a large number of responsive myeloma patients followed without treatment. Results were correlated with a variety of clinical variables in order to identify those characteristics associated with long durations of disease stability.

In comparison with patients not receiving drug treatment until relapse, the survival time of responding patients was not prolonged with indefinite courses of melphalan-prednisone or BCNU-prednisone after the first year. Patients receiving melphalan-prednisone had a slightly higher frequency of a high tumor mass grade and a slightly lower incidence of a marked tumor reduction from their initial treatment. These features might account for the longer survival for some of the patients assigned to no therapy in comparison with those given melphalan-prednisone (Fig. 1). The differences among the patient groups were not considered so marked as to suggest that a longer survival for the treated patients might have occurred with more similar treatment groups. A more important factor contributing to the prolonged survival of patients assigned to the no-treatment group was the high frequency of tumor recontrol after the resumption of melphalan-prednisone during relapse. Thus as in patients with Hodgkin disease⁹ and chronic myelogenous leukemia¹⁰ the first relapse appeared to result from a tumor subclone that was still sensitive to chemotherapy. Since all of these patients had also responded to their initial therapy, a growth

advantage for a drug-sensitive tumor population was evident in them.⁷ Following the resumption of treatment, the magnitude of tumor reduction was usually less, and the duration of remission shorter, than that present after the initial 12 mo of therapy. Eventually, progressive tumor growth of a resistant cell population became apparent with a tumor doubling time similar to that noted during the first relapse.

Specific disease features were identified that were associated with long or short durations of unmaintained disease control. Patients with pretreatment characteristics associated with a low tumor mass or those with disappearance of serum myeloma proteins had the longest remission times. For 16 patients with either of these features who were considered to have very low numbers of plasma cells after 1 yr of chemotherapy the median duration of remission was 19 mo; 10 of 12 such patients with evaluable trials achieved tumor recontrol following melphalan-prednisone treatment during relapse. In those patients with disappearance of myeloma proteins, tumor regrowth was undoubtedly occurring for many months before recurrence of the monoclonal globulin was recognized on the electrophoretic strip. More sensitive techniques using idiotype antibody may be useful in defining the kinetics of tumor reduction and regrowth in these patients.¹¹ Patients presenting with a high or intermediate tumor mass grade, or with persistent serum myeloma proteins after 12 mo of therapy, had short durations of unmaintained remission. Such patients should receive continued courses of melphalan-prednisone during remission rather than being followed without therapy. Long-term followup without chemotherapy should be considered only when the serum myeloma protein has disappeared and for those with a low tumor mass in whom Bence Jones protein can no longer be detected. The rate of tumor growth also has an important influence on survival, so that patients with a longer tumor doubling time were likely to have a longer survival;⁸ such patients were also more likely to achieve second remissions from melphalan-prednisone than patients with more rapid tumor growth.

These observations emphasize the importance of an accurate pretreatment staging of tumor mass and serial evaluations of myeloma proteins during therapy in order to identify those responding patients in whom long durations of disease stability without treatment are likely. In addition, periodic electrophoretic studies are essential, even when the abnormal protein can no longer be detected, in order to confirm early relapse and the need to resume melphalan-prednisone therapy.

Acute leukemia has been reported in many patients with multiple myeloma,¹² occurring in 6% of responding patients living longer than 2 yr.¹³ An oncogenic effect from alkylating agent therapy has been implicated as a major etiologic factor because most patients received at least 3 yr of treatment, the frequency of leukemia after such therapy is much higher than in normal individuals¹³ or in untreated patients,¹⁴ and major cytogenetic changes were usually observed in the leukemic cells.¹³ The considerable benefits from melphalan-prednisone chemotherapy far outweigh this hazard in more than 90% of patients found to have multiple myeloma, yet certain patient groups have now been identified where the utility of indefinite alkylating agent chemotherapy must be ques-

tioned, including selected asymptomatic patients with indolent disease who may remain stable without chemotherapy for several years¹⁵ and patients with overt myeloma who develop marked reductions in plasma cell number after treatment. The periodic reassessment of each patient's symptomatic status, tumor mass load,^{4,5} and rate of tumor mass change^{7,8} must be considered in justifying the need for indefinite alkylating agent therapy. Thus melphalan should be withheld from patients with disappearance of their serum myeloma protein following at least 1 yr of treatment, reinstituted for rising proteins, and then replaced by Adriamycin combination therapy when tumor resistance becomes evident.¹⁶

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