COMBINATION THERAPY FOR MULTIPLE MYELOMA

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The effect of six different chemotherapy regimens were evaluated in 462 previously untreated patients with multiple myeloma. In comparison with other treatments, drug combinations that included vincristine and were given at 3-week intervals were associated with higher response rates and longer survival times. No gain was noted from the use of Adriamycin or from combinations of alkylating agents unless vincristine was given and the treatment intervals were short. Seventy-one responding patients were allocated at random to maintenance treatment with intermittent courses of either azathioprine–prednisone or a combination of melphalan–cyclophosphamide–carmustine (BCNU)–prednisone. The survival time was not prolonged with either maintenance treatment in comparison with that for responding patients continued on other therapies or on no therapy in previous studies. Attempts to reduce tumor mass maximally with a change in the therapeutic modality, such as with immunotherapy or radiotherapy, remain to be evaluated.

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INTERMITTENT COURSES OF MELPHALAN AND prednisone have reduced tumor mass in a large fraction of patients with multiple myeloma.[6,7] The addition of procarbazine, with or without vincristine, to the melphalan–prednisone combination did not improve the response rate, although patients receiving vincristine had the longest survival time yet noted in the Southwest Oncology Group (SWOG).[5] Since vincristine alone reduced tumor mass further in some responsive myeloma patients,[15] the role of this antimitotic drug was reevaluated as part of the initial therapy in a large number of additional patients. Results indicated a slight superiority in both response rate and survival time from two different drug combinations that included vincristine.

Adriamycin is an anthracycline antibiotic with proven activity in patients with a variety of malignancies. This drug had produced remissions in patients with myeloma resistant to melphalan–prednisone,[1,3] as well as in previously untreated patients.[3] This study evaluated Adriamycin combinations with alkylating agents and prednisone in a large number of previously untreated patients with multiple myeloma. Only when vincristine was included in the combination did the results support a useful role for Adriamycin as part of the initial treatment for this disease.

The median remission duration for patients with myeloma responding to melphalan-prednisone was about 2 years.[4] In a previous SWOG study, the survival of groups of responding patients receiving intermittent melphalan–prednisone or BCNU–prednisone was similar to that of patients followed without any chemotherapy.[5] This report summarizes experiences with two additional maintenance therapies, one

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TABLE 1. Frequency of Response from Different Drug Combinations in Multiple Myeloma

	No. treated	Not evaluable: Early death	Not evaluable: Inadequate report	No. evaluable	No. responsive	Response rate* (% evaluable)	(% All)
M+A+P (1/73 – 9/74) Melphalan 6 mg/m²/day × 4 Adriamycin 25 mg/m²/on day 1 Prednisone 60 mg/m²/day × 4 q 4 weeks	76	6	3	67	26 (5)†	46	41
M+C+P (1/73 – 9/74) Melphalan 6 mg/m²/day × 4 Cyclophosphamide 500 mg/m² i.v. day 1 Prednisone 60 mg/m²/day × 4 q 4 weeks	84	8	2	74	33 (2)	47	42
M+C+B+P (1/73 – 9/74) Melphalan 4 mg/m²/day × 4 Cyclophosphamide 300 mg/m² i.v. day 1 BCNU 30 mg/m² i.v. day 1 Prednisone 60 mg/m²/day × 4 q 4 weeks	75	4	1	70	27 (7)	49	45
C+A+P (10/74 – 2/76) Cyclophosphamide 100 mg/m² p.o./d × 4 Adriamycin 25 mg/m² i.v. day 1 Prednisone 60 mg/m² p.o./d × 4 q 3 weeks	64	2	3	59	19 (4)	39	36
V+C+A+P (10/74 – 8/76) Vincristine 1.0 mg i.v. day 1 Cyclophosphamide 100 mg/m² p.o./d × 4 Adriamycin 25 mg/m² i.v. day 2 Prednisone 60 mg/m² p.o./d × 4 q 3 weeks	77	3	0	74	32 (10)	57	55
V+M+C+P (10/74 – 8/76) Vincristine 1.0 mg i.v. day 1 Melphalan 5 mg/m² p.o./d × 4 Cyclophosphamide 100 mg/m² p.o./d × 4 Prednisone 60 mg/m² p.o./d × 4 q 3 weeks	86	1	8	77	41 (7)	62	56
TOTAL	462	24	17	421	178 (35)	51	46

* Includes slow responders during crossover treatments.

† Parentheses indicate number of additional patients responding during crossover treatments after initial 6 months.

with azathioprine–prednisone and the second with a combination of melphalan–cyclophosphamide–carmustine (BCNU)–prednisone. Azathioprine is an antimetabolite active against rodent plasmacytomas[17] that might be effective against a residual myeloma cell population with an increased growth fraction.[15] Treatment with a combinaton of different alkylating agents has also been reported as more effective than melphalan alone.[14] Results did not indicate any therapeutic advantage for long-term maintenance treatment with either azathioprine or alkylating agent combinations in comparison with previous SWOG regimens.

MATERIALS AND METHODS

This report presents an analysis of 462 consecutive patients with multiple myeloma treated at 14 Southwest Oncology Group institutions between January, 1973 and August, 1976. Only patients previously untreated for myeloma were included. The diagnosis was based on bone marrow plasmacytosis exceeding 10% and a myeloma globulin peak on serum or urine electrophoresis in symptomatic patients; 10 patients without detectable peaks (2%) were also included when marrow plasmacytosis, lytic bone lesions, and depression of normal serum immunoglobulins were present.

Treatment Regimens

Between January, 1973 and September, 1974, 235 patients were assigned at random to one of three different combinations of melphalan and prednisone. As indicated in Table 1, 76 patients received a melphalan–Adriamycin–prednisone combination (MAP), 84 were treated with melphalan–cyclophosphamide–prednisone (MCP), and 75 received melphalan–cyclophosphamide–BCNU–prednisone (MCBP). These treatments were given in doses outlined in Table 1 and were repeated at 4-week intervals. Patients unresponsive to MAP after 6 months of initial therapy received MCBP for an additional 6 months; pa-

tients unresponsive to MCP or MCBP were treated with MAP.

As preliminary analyses indicated similar response rates of 46–49% from all treatments, with recovery in granulocyte and platelet counts after 3 weeks in many patients receiving MCP and MAP, an additional 227 patients were assigned at random to one of three additional drug combinations between October, 1974 and August, 1976. As indicated in Table 1, 64 patients received a cyclophosphamide–Adriamycin–prednisone combination (CAP), 77 were treated with a vincristine–cyclophosphamide–Adriamycin–prednisone combination (VCAP) and 86 received a vincristine–melphalan–cyclophosphamide–prednisone combination (VMCP). These treatments were given at 3-week intervals. Patients unresponsive to CAP or VCAP after 6 months of initial therapy received VMCP for an additional 6 months; patients unresponsive to VMCP were treated with VCAP. Treatment with the CAP combination was terminated in February 1976 after a response rate of 39% was noted. All patients received treatments in doses adjusted to produce bone marrow toxicity (e.g. nadir in granulocytes between 1000–)0/mm^3).

aluation of Response

Response was evaluated no sooner than 4 eks after the start of therapy. The effect of treatment could not be evaluated in patients who died during the first 4 weeks, who were considered to have had early deaths. Clinical response was based on criteria previously presented in detail that required both of the following sustained for at least two months: 1) a decrease in the production rate of serum myeloma protein to less than 25% of the pretreatment value, and 2) disappearance of Bence Jones protein excretion.[5,6] Calculations of the serum myeloma protein production rate required considerations of the serum concentration of myeloma globulin, the plasma volume, and the catabolic rate of the myeloma globulin as affected by the serum concentration.[16,19] Previous studies had demonstrated that changes in tumor mass were underestimated when calculations did not consider the changing catabolic rate of IgG globulins and changing plasma volume.[6,16]

Remission Maintenance

Between July, 1973 and March, 1975, 71 consecutive responding patients were assigned at random to one of two maintenance regimens after 6 months of initial chemotherapy with MAP, MCP, or MCBP as described previously (Table 2). Each patient was eligible for randomization provided he had received at least four courses of chemotherapy and was alive and in remission 6 months after the institution of treatment. Twenty-four eligible patients were not registered at all or randomized later than 5 months after their eligibility had been confirmed, primarily because of uncertainty as to whether a remission had been achieved or because they had been lost to follow-up when due for randomization; these patients were excluded from the analysis. Of the 71 eligible patients who were randomized on schedule, 20 had responded to MAP, 24 to MCP, and 27 to MCBP. After the durations of remission and survival were found to be similar for each group of responding patients, all patients receiving the three induction regimens were analyzed together within their specific maintenance group. Maintenance regimens included either 1) indefinite courses of MCBP at 4-week intervals, or 2) intermittent courses of azathioprine–prednisone at 3-week intervals with an MCBP reinforcement course given after every four courses of azathioprine–prednisone (Table 2). Treatments were continued until death or unequivocal evidence of myeloma protein relapse.

TABLE 2. Responsive Patients Eligible for Remission Maintenance

No. patients responding to initial therapy:	86	
No. additional patients responsive to crossover treatment after 6 mos.:	14	
Total no. of responsive patients:	100	
Ineligible for randomization because of death or relapse within 6 months:		5
Tumor relapse	2	
Death from renal failure	3	
Eligible for randomization:		95
Eligible, but not randomized within 5 mos.	24	
No. eligible patients randomized within 5 mos. of eligibility:		71

Maintenance treatment	No. randomized	No. dead
M+C+B+P		
Melphalan 4 mg/m^2/day × 4	36	19
Cyclophosphamide 300 mg/m^2 i.v. day 1		
BCNU 30 mg/m^2 i.v. day 1		
Prednisone 60 mg/m^2/day × 4 q 4 weeks		
I+P		
Azathioprine 125 mg/m^2 p.o./d × 7	35	12
Prednisone 40 mg/m^2 p.o./d × 7 q 3 weeks		
One MCBP course given q 4 I+P courses		

TABLE 3. Comparability of Patient Groups

	Remission induction treatments						Maintenance treatments		
	MAP	MCP	MCBP	CAP	VCAP	VMCP	IP	MCBP	Historical†
No. patients	76	84	75	64	77	86	35	36	136
Age, yr (median)	62	58	60	59	60	63	58	58	58
Sex (% male)	66	60	60	67	53	56	60	58	64
Race (% black)	25	24	21	22	17	21	17	19	15
Pretreatment abnormalities (% of total)									
Hemoglobin <8.5 g/100 ml	30	23	32	11	21	30	17	28	24
Corrected calcium* >11.5 mg/100 ml	20	18	33	23	20	26	24	17	18
BUN >40 mg/100 ml	18	10	14	14	11	6	3	6	15
Tumor mass grade									
% High	41	40	44	36	36	54	31	44	41
% Intermediate	41	42	27	41	39	36	43	25	28
% Low	18	18	29	23	25	10	26	31	31

* Corrected calcium (mg/100 ml) = serum calcium (mg/100 ml) − serum albumin (g/100 ml) + 4.0.
† Includes all responding patients from a previous study.[5]

Results were compared with a group of 111 responding patients treated with other maintenance programs in a previous study.[5] These patients had been assigned at random to either melphalan–prednisone, BCNU–prednisone, or no treatment after 12 months but their survival times were calculated from the sixth month for this comparison; an additional 25 patients were included who had been alive and in remission after 6 months but who relapsed or died before they were eligible for maintenance therapy after 12 months (total historical group 136 patients). Patients responding after 6 months of treatment with CAP, VCAP and VMCP received a 12-month program of chemoimmunotherapy using alternating BCG immunotherapy and VMCP chemotherapy, but definitive results from this maintenance program remain to be evaluated.

Survival and Remission Duration Analyses

All patients were included in the survival calculations that used the life table method from the start of both induction and maintenance chemotherapy until death.[12] The times from *randomization* to relapse were also calculated for the groups of patients assigned to the different maintenance groups.

RESULTS

Comparability of Treatment Groups

The frequency and severity of specific disease complications were evaluated in each group of patients receiving the different induction or maintenance treatments evaluated in this study (Table 3). The absolute tumor mass before the start of chemotherapy was defined in each patient from clinical criteria described elsewhere.[4,9] In essence, patients were assigned to either a high, intermediate, or low tumor mass grade in accordance with the degree of anemia, hypercalcemia, serum myeloma protein level, and the extent of lytic bone lesions. There were no major differences between most treatment groups in those major clinical or laboratory characteristics known to affect prognosis.[4] Severe anemia and a high tumor mass grade were more frequent, and azotemia was less common, in patients receiving VMCP than in those randomized to the other treatments. The 41 patients excluded from the analysis of response rate because of early death or inadequate data had a much higher frequency of all of the harmful prognostic factors with 67% presenting with a high tumor mass grade; 43% had a hemoglobin less than 8.5 g/100 ml, 35% had hypercalcemia and 26% had azotemia with a BUN exceeding 40 mg/100 ml.

Frequency of Response

Of 462 patients who received one of six different combinatons of an alkylating agent with prednisone, the records of 421 could be evaluated. Response could not be defined in 41 patients: in 24 (5%) because death occurred within

4 weeks after the institution of therapy and in 17 (4%) because of inadequate data. Remission was confirmed in different percentages of patients receiving each of the six different induction regimens (Table 1). Four treatment groups had similar frequencies of remission ranging between 39–49%. However, the response rate for VMCP given at 3-week intervals was 15% higher than that for MCP prescribed at 4-week intervals ($p < 0.10$); the response rate for VCAP was 18% higher than that for CAP ($p < 0.10$), both treatments given at 3-week intervals (Table 1). Thus, the improvement in response rate for both groups of patients receiving vincristine was slight but reproducible.

More than 80% of responding patients achieved a 75% reduction in serum myeloma protein production and/or disappearance of Bence Jones protein within the first 6 months. Sixteen percent of responding patients did not reduce their myeloma protein to the level consistent with remission until after 6 months while on a "crossover treatment" (Table 1). In all patients responding slowly while on a crossover treatment, the rate of decline in myeloma protein production remained unchanged.

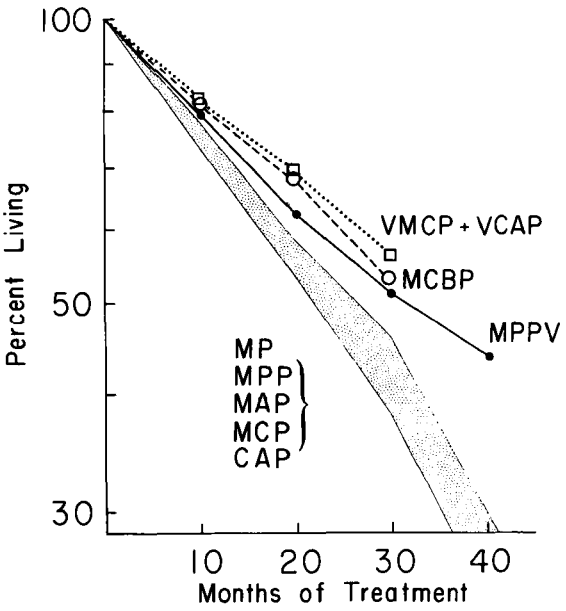

FIG. 1. Survival from initial treatment for all patients assigned to combination therapies with vincristine in this (VMCP and VCAP) and one previous study (MPPV). Results were compared with curves calculated for patients receiving MCBP treatment and five other treatments that fell within the stippled range.

Survival Time

Survival curves were calculated for all patients receiving each of the induction therapies. Results were compared with those from 574 patients receiving intermittent melphalan–prednisone (MP), melphalan–prednisone–procarbazine (MPP), or melphalan–prednisone–procarbazine–vincristine (MPPV) between 1965–1972.[5,6,7] Five of the survival curves were similar and fell within the stippled range on Figure 1, all being superior to that from intermittent melphalan alone.[7] Analyses to date indicated slightly longer survival times for patients receiving vincristine in one previous SWOG regimen (MPPV), and in the two groups of patients receiving vincristine and alkylator agent combinations at 3-week intervals in this study (VMCP and VCAP); patients receiving the MCBP treatment combination also had a longer survival time. The survival for all 305 patients receiving vincristine combinations (VMCP, VCAP, MPPV) was significantly longer than that for the 727 patients receiving six different alkylator-prednisone combinations without vincristine (MP, MPP, MCP, MAP, MCBP, CAP) ($p < .01$). No other differences were significant. The projected median survival for all patients on the VMCP and VCAP combinations was 34 months, about 9 months longer than that for patients on five previous combinations of alkylating agents and prednisone (stippled range in Fig. 1).

Remission Maintenance

Remission duration and survival were compared for groups of responding patients after random allocation to either intermittent MCBP therapy or intermittent azathioprine–prednisone with periodic MCBP reinforcement (Table 2). All patients were in remission at the time of randomization, which was no sooner than 6 months after the start of induction therapy. Of 71 eligible, responsive patients who were randomized on schedule, 36 received indefinite courses of intermittent MCBP, and 35 were treated with azathioprine–prednisone. Results were compared with those from 136 responding patients maintained on other SWOG regimens after the first 6 months. Table 3 confirms the comparability of these patient groups in terms of those major factors known to affect prognosis.[4] As indicated in Fig. 2, the survival times from randomization for the IP and MCBP groups were similar to that for patients maintained on previous therapy programs after the sixth month. The remission durations from randomization were also similar for all treatments.

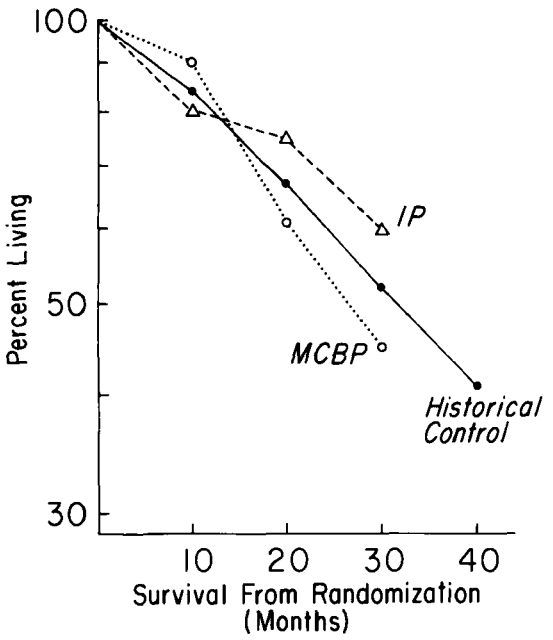

FIG. 2. Survival from randomization after 6 months of initial therapy for 36 responding patients maintained on MCBP (open circles) and 35 on azathioprine-prednisone (open triangles), in comparison with 136 responding patients receiving previous therapies (solid circles).

DISCUSSION

This report summarizes the effects of six different drug combinations in 462 patients with multiple myeloma treated at 14 SWOG institutions over a 4-year period. All patients had unequivocal criteria for the diagnosis of myeloma and received intermittent courses of chemotherapy in maximal doses. All of the six patient groups were considered comparable in view of the similar frequency and severity of those disease complications known to affect prognosis.[4] Response to therapy was based on a 75% reduction in serum myeloma protein production rate and the elimination of Bence Jones protein, as described previously.[5,6] Since the rate of decline in myeloma protein production remained unchanged during crossover treatments, those few patients who responded slowly after 6 months were analyzed within their initial treatment group.

Vincristine is an antimitotic drug, which has reduced tumor mass further in several myeloma patients treated during remission,[15] presumably from the destruction of an increased fraction of dividing cells. Vincristine may also enhance the penetration and accumulation of certain drugs within cancer cells, as shown recently for methotrexate.[10] This report documents a response rate that was about 15% higher when vincristine was added to alkylating agent–prednisone combinations given at 3-week intervals. In fact, both the VCAP and the VMCP treatments produced the highest response rates yet noted by the SWOG in patients with multiple myeloma (i.e., 57 and 62%). In addition, preliminary analyses showed that the survival times were longer with each of the vincristine treatment combinations, in comparison with the comparable treatment programs without this drug. Vincristine was given in a low dose on the day prior to the onset of other therapies in an attempt to synchronize tumor cells.[13] Neurotoxicity was rare, mild when it occurred, and reversible. Thus, it seems reasonable to include vincristine as part of the initial chemotherapy program for all patients with multiple myeloma. Shortening the treatment interval from 4 weeks to 3 weeks may also have improved our results by allowing the administration of larger total doses of chemotherapy. Finally, the lower incidence of severe renal failure and the improving management of certain disease complications may also have contributed to the longer longevity from the VMCP and VCAP treatments.

Combinations of different alkylating agents were evaluated in an attempt to achieve more frequent and more prolonged reductions of the myeloma cell mass. Bergsagel *et al.* had reported remissions from cyclophosphamide in patients resistant to melphalan,[8] suggesting that cross-resistance to these drugs was not present in all patients. Lee *et al.* found that the combination of low doses of BCNU and vincristine, with moderate doses of melphalan, cyclophosphamide, and prednisone, produced a response rate and survival time superior to that resulting from previous trials using melphalan–prednisone.[14] Both the MCP and the MCBP combinations evaluated by the SWOG produced a frequency of remission similar to that from previous treatments, suggesting that combinations of alkylating agents do not provide any therapeutic advantages. The higher response rates and longer survival times from the VMCP and the VCAP programs, that could be repeated at 3-week intervals, suggested that certain drug combinations were superior provided that the treatment intervals were short and that vincristine was included in the combination.

Adriamycin is an agent with proven activity in patients with leukemia, lymphoma, and a variety of other malignancies. Therapeutic activity has been noted in some patients resistant to melphalan–prednisone;[1,3] combinations of Adriamycin with BCNU have produced second

remissions in some patients with relapsing myeloma.[2] The combination of cyclophosphamide and Adriamycin was synergistic in the therapy of rodent leukemia.[18] Yet, in the dose regimens used here, no improvement was observed in the frequency of remission or in the survival time when Adriamycin was added to combinations of melphalan–prednisone or cyclophosphamide–prednisone as part of the initial treatment. Only when vincristine was included in the Adriamycin combination and the treatment intervals were short, was a high response rate confirmed in previously untreated patients.

The effects of two different programs of remission maintenance therapy were evaluated in a large number of patients who had responded to their initial treatment. Cohorts of responding patients were allocated at random either to continued azathioprine–prednisone with periodic MCBP reinforcement courses or to repeated courses of MCBP, provided that they were in a remission status by quantitative protein criteria at least 6 months after the start of therapy. Azathioprine was evaluated on the possibility that the larger growth fraction present in the myeloma population during remission might be susceptible to an antimetabolite.[15] Also, azathioprine had shown therapeutic activity against certain plasma cell tumors in rodents,[17] and in some patients with multiple myeloma.[11] The combination of MCBP was evaluated during remission after encouraging results had been reported from a similar regimen in previously untreated patients.[14] Results were compared with those from a large group of comparable responding patients maintained on previous SWOG treatments. No improvements were found in either remission duration or survival time, and no advantage was apparent from these programs of long-term MCBP or azathioprine–prednisone maintenance.

In multiple myeloma, the duration of remission and survival is directly related to the number of abnormal plasma cells remaining after an optimum program of treatment.[4,9] Prolonged maintenance therapy is unlikely to be helpful unless a greater degree of tumor reduction occurs. Rather than supporting indefinite chemotherapy, these observations justified the evaluation of other treatment modalities during remission, such as cycleactive agents, immunotherapy or radiotherapy, that might be more likely to produce greater degrees of tumor reduction.

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