Chemoimmunotherapy for Multiple Myeloma

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The effect of chemoimmunotherapy consolidation treatment using alternating courses of alkylating agents and BCG was studied in 105 responding patients with multiple myeloma. The survival time of these patients was similar to that of responding patients treated on previous maintenance programs, indicating no apparent value from BCG for myeloma. The duration of unmaintained remission was longest in those with low numbers of residual plasma cells, and relapse usually developed within one year in patients with persistent serum myeloma peaks. Disease recontrol was achieved in 50% of relapsing patients whose median survival from retreatment was 20 months. Patient follow-up without chemotherapy until relapse was justified mainly for those responding patients with disappearance of myeloma proteins.

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THE MEDIAN SURVIVAL time for patients with multiple myeloma who have responded to chemotherapy is about two years longer than that of unresponsive patients, a prolongation in life span that has been accounted for by the remission duration.[1] Survival was not improved in patients who received melphalan-prednisone courses indefinitely in comparison with patients who had been followed without therapy until relapse.[2] These similar results were attributed to the high frequency of second remissions in patients relapsing on no treatment in that study. Repeated azathioprine-prednisone courses given on the possibility that an increased percentage of dividing cells may be destroyed by an antimetabolite also failed to confer any survival benefit.[3]

Between 1975 and 1978, the Southwest Oncology Group (SWOG) evaluated the utility of a chemoimmunotherapy program that combined a melphalan-prednisone combination with Bacillus Calmette-Guerin (BCG) vaccine in responding patients. BCG consolidation, in combination with chemotherapy, had been associated with survival prolongation in melanoma[9] and acute leukemia[10] but had not been evaluated in myeloma. This report indicates that no survival benefits were observed by adding BCG to chemotherapy for consolidation therapy in patients with myeloma. After the completion of treatment, the duration of unmaintained remission was longest in those patients with very low numbers of plasma cells. Retreatment with a melphalan-prednisone combination during relapse was followed by a median survival time of 20 months despite the occurrence of second remissions in only one half of the patients.

Methods

This report presents an analysis of 289 consecutive patients with multiple myeloma whose treatment began at 12 SWOG institutions between October 1974 and February 1977. Only patients previously untreated for myeloma were included in the study. The diagnosis was based on criteria defined by the Chronic Leukemia-Multiple Myeloma task force that included bone marrow plasmacytosis and a myeloma globulin peak on serum or urine electrophoresis in symptomatic patients[7]; seven patients without detectable peaks (2%) on immunoelectrophoresis were also included when marked bone marrow plasmacytosis, lytic bone lesions, and marked depression of normal serum immunoglobulins were present. The pretreatment tumor mass was rated as high, intermediate, or low in accordance with a clinical staging system described previously.[4,8]

For the Southwest Oncology Group.

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TABLE 1. Response and Survival from Different Drug Combinations in Multiple Myeloma

	No. treated	Early death	Inadequate report	No. evaluable	No. responsive	Response rates % Evaluable	Response rates % All	Median survival (months)
Courses every 3 weeks								
C + A + P								
Cyclophosphamide, 100 mg/m², p.o./d × 4 Adriamycin, 25 mg/m², i.v., day 1 Prednisone, 60 mg/m², p.o./d × 4	57	2	1	54	26	48	46	32
V + C + A + P								
Vincristine, 1.0 mg, i.v., day 1 Cyclophosphamide, 100 mg/m², p.o./d × 4 Adriamycin, 25 mg/m², i.v., day 1 Prednisone, 60 mg/m², p.o./d × 4	87	3	1	83	56	67	64	32
V + M + C + P								
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	94	1	6	87	52	60	55	30
V + B + A + P								
Vincristine, 1.0 mg, i.v., day 1 BCNU, 25 mg/m², i.v., day 1 Adriamycin, 25 mg/m², i.v., day 1 Prednisone, 60 mg/m², p.o./d × 4	51	3	0	48	31	65	61	32

Treatment Regimens

All patients were assigned at random to a combination of either cyclophosphamide-Adriamycin-prednisone (CAP), vincristine-cyclophosphamide-Adriamycin-prednisone (VCAP), or vincristine-melphalan-cyclophosphamide-prednisone (VMCP) in the dose regimens described in Table 1. After a lower response rate to the CAP combination was found, a vincristine-BCNU (Bis-chlorethylnitrosourea)-Adriamycin-prednisone regimen (VBAP) was substituted in the randomization scheme. All patients received doses adjusted to produce moderate degrees of bone marrow toxicity (*i.e.*, a nadir in granulocytes between 1000 and 2500/mm³ or in platelets between 50,000 and 100,000/mm³) between courses that were repeated at three-week intervals. Clinical response was based on criteria previously described and based on a 75% reduction of myeloma protein production rate.[3]

Remission Maintenance

Between April 1975 and January 1978, 105 eligible responding patients who had received at least six months of drug treatment on any of the four induction regimens described above were assigned to a chemoimmunotherapy program consisting of alternating cycles of VMCP and BCG for 12 more months (Table 2). Three patients were ineligible for this chemoimmunotherapy program since they were randomized to receive treatment later than five months following their eligibility. Of the 105 eligible responding patients who were registered, 19 had been induced into remission with CAP, 32 with VCAP, 34 with VMCP, and 20 with VBAP. Because the survival times for responders in the different groups were similar, all eligible patients registered on VMCP-BCG maintenance were combined in the analysis. The consolidation treatment consisted of one VMCP course given every three

TABLE 2. Schema of Treatment

Randomize for 6 months of treatment	Responding patients	Still in remission after 12 months of BCG	Relapse
CAP VCAP VMCP VBAP	VMCP + BCG for 12 months	→ No treatment until relapse	→ Resume VMCP

A = Adriamycin; B = BCNU; C = Cytoxan; M = melphalan; P = prednisone; V = vincristine.

to four weeks in doses previously described (Table 1); 2×10^8 attenuated Pasteur-strain BCG organisms were given by scarification 8 and 15 days after the start of each VMCP course. Treatment continued for 12 months, after which no chemotherapy was given to those still in remission until there was evidence of relapse (Table 2). When relapse developed, the VMCP combination was reinstituted and continued until the patient relapsed or died. Relapse was defined by the earliest of either an increase in myeloma protein production to more than 25% of the pretreatment value, a doubling of myeloma protein production, the reappearance of myeloma proteins that had disappeared, or unequivocally progressive lytic bone lesions. The frequency of second reductions in tumor mass was defined in 20 patients with evaluable data at the M. D. Anderson Hospital; results were compared with those in 13 patients relapsing after unmaintained remission periods that followed only one year of initial chemotherapy in a previous study.[2]

The survival of responding patients who received BCG was compared with those maintained on monthly courses of either a melphalan-cyclophosphamide-BCNU-prednisone combination (MCBP) or an azathioprine-prednisone combination (IP) with MCBP reinforcement in a preceding SWOG study.[3] All eligible and registered patients were included in the survival calculations that used the life table method from the start of both the initial and the maintenance chemotherapy until death.[14]

Delayed Hypersensitivity Studies

Delayed hypersensitivity was evaluated from the magnitude of skin induration to test antigens in 42 previously untreated patients with multiple myeloma older than 40 who were studied at the M. D. Anderson Hospital. Patients were selected when an outpatient evaluation over several days was possible, when no corticosteroid or radiotherapy was necessary, and when the same technician was available to quantify all results. Five patients were included who had received local radiotherapy more than four months previously. The antigens used were dermatophytin, streptococcal varidase, candida, mumps, PPD, and KLH using preparations, doses, and techniques of injection described previously.[16] The maximum induration as an average of two right angle measurements was recorded in millimeters 24 and 48 hours following the intracutaneous injection of test substances; the maximum response was compared with those from a control group of healthy volunteers over the age of 40 studied at the same institution.[16] Multiple assessments of the skin test reaction were conducted in 32 myeloma patients among whom were 20 responsive and 12 unresponsive patients. No chemotherapy had been given for at least four weeks before any follow-up skin test.

TABLE 3. Comparability of Patient Groups on Different Maintenance Treatments

	VMCP-BCG	Azathioprine*	MCBP*
No. patients	105	33	33
Age, yr. (median)	61	61	58
Sex (% male)	64	58	58
Race (% black)	18	18	21
Pretreatment abnormalities (% of total)			
Hemoglobin (<8.5 g/100 ml)	11	12	21
Serum calcium (>11.5 mg/100 ml)	15	18	9
BUN (>40 mg/100 ml)	8	3	9
Tumor mass grade			
% High	37	30	43
% Intermediate	40	46	27
% Low	23	24	30

* Includes all patients maintained on these regimens in a previous study.[2]

Results

Remission Maintenance

The response rates for patients who received one of three initial treatment combinations that included vincristine ranged from 60–67% in comparison with 48% for CAP treatment (Table 1). Further details on the effects on these treatments have been described previously.[3]

The survival time was evaluated in 105 responding patients who received a VMCP-BCG chemoimmunotherapy combination. Results were compared with those of 66 responding patients from the same institutions maintained until relapse on either an azathioprine-prednisone or an MCBP combination after the first six months.[3] Table 3 confirms the similarity of the three patient groups in those major factors known to affect prognosis. Bacillus Calmette-Guerin produced mild to moderate local skin reactions at the scarification site in all patients; treatment was terminated in three patients because of generalized reactions such as diffuse papular eruption (two patients) or recurrence of active tuberculosis (one patient). As indicated in Figure 1, the median survival for patients receiving BCG was 38 months, a duration about five months longer than that from the other treatments.

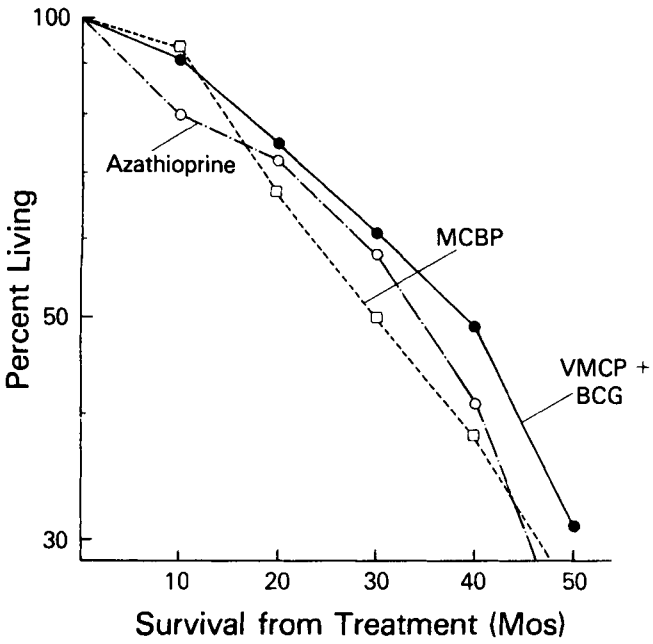

FIG. 1. Survival time from start of remission maintenance treatment for 105 responding patients who received a VMCP-BCG chemoimmunotherapy regimen for 12 months. Results were compared with those in 66 responding patients maintained previously until relapse on either azathioprine-prednisone or an MCBP combination.

This superiority was not significant ($P > 0.2$), and the longevity from all programs was also similar to that for 64 responding patients followed without treatment or continued on melphalan-prednisone in a previous SWOG study.[2]

Unmaintained Remissions

Of the 105 patients who received the VMCP-BCG program, 30 relapsed or died during the 12-month period of remission maintenance, and patients with a persistent serum peak constituted 24 of these patients. Thirty-four of the 40 patients with disappearance of myeloma proteins on cellulose acetate electrophoresis completed the 12-month chemoimmunotherapy program, including 16 with disappearance of only Bence Jones protein as evaluated by electrophoresis of urine concentrates (Table 4). Follow-up data were available to evaluate the duration of unmaintained remission in 69 patients, of whom 14 were still alive in remission, four died in remission of unrelated disease, and 51 relapsed from myeloma. Six patients without an abnormal protein at diagnosis were excluded because their unmaintained remission time could not be measured precisely. The median duration of unmaintained remission for all patients was nine months, and longer periods of disease stability were found mainly in patients with disappearance of myeloma protein (Table 4). Withholding chemotherapy in patients with a persistent peak was usually followed by rising levels of the monoclonal component within 12 months.

TABLE 4. Correlation of Unmaintained Remission Time with Myeloma Cell Mass

	No. patients	Unmaintained remission duration (median mo.)
All evaluable patients*	69	9
Pretreatment tumor mass		
High and intermediate		
All patients	56	8
Serum peak persists	33	6
Serum peak disappears	12	11
Bence Jones protein disappears	11	10
Low		
All patients	13	14
Serum peak persists	2	6
Serum peak disappears	6	21
Bence Jones protein disappears	5	12

* Six additional patients never had a myeloma protein, and their unmaintained remission times could not be measured.

Reinduction Therapy

When chemotherapy was resumed in 20 relapsing patients with rising myeloma proteins treated at the M. D. Anderson Hospital, a greater than 50% reduction of myeloma cell mass occurred in ten. Thus, second partial remissions developed in 50% of the relapsing patients in this study, in comparison with 77% of those relapsing in a previous study,[2] but this difference was not significant ($P > 0.2$). Patients who relapsed after six months of unmaintained remission had a higher frequency of tumor recontrol (6/8) than patients who relapsed within the first six months of no treatment follow-up (4/12). The frequency of disease recontrol was similar in all patient groups in Table 4, regardless of the pretreatment tumor mass or the myeloma protein status. The median survival from the resumption of chemotherapy was 20 months, a duration similar to that of 15 months for patients retreated after relapsing with only one year of initial chemotherapy.[2] Figure 2 demonstrates the prolonged tumor mass stability and survival time in two patients rated as unresponsive to retreatment with VMCP.

Skin Tests

The median diameter of induration from each of the antigens evaluated in 42 patients before chemotherapy was virtually identical to those found in normal subjects of similar age (Table 5). No correlation was noted between the intensity of the reaction to any of the antigens tested and the pretreatment tumor mass, the likelihood of response, or the survival time. The effects of chemotherapy were evaluated on the skin test re-

action in 32 patients with follow-up studies. No consistent correlations were apparent between the follow-up skin test reactions and either response or survival. When it developed, myeloma protein relapse was not associated with any consistent changes in skin test reactions. Responsive patients who received BCG usually improved their response to PPD; 12 of 15 patients so treated tripled their mean diameter of induration to more than 15 mm, a change that never occurred in any unresponsive patient not given BCG.

Discussion

Recent SWOG studies have shown that 60% of patients with multiple myeloma achieved remissions as defined by a 75% or greater reduction in myeloma protein production rate.[3] In these trials, the response rate was about 15% higher and the median survival time about five months longer when vincristine was included in the drug combination, and the treatments were repeated at three-week intervals. This report indicates that a similar high response rate resulted from a combination of vincristine-BCNU-Adriamycin-prednisone (VBAP), a regimen that also produced 50% reductions in tumor load in about 30% of relapsing patients.[5]

A large number of responding patients received a 12-month consolidation treatment using a VMCP-BCG combination to enhance patient immunity. The VMCP drug combination was chosen because this treatment had produced the highest response rate in a previous SWOG study.[3] Chemoimmunotherapy using BCG has been associated with the prolongation of survival and remission in patients with malignant melanoma,[9] acute leukemia,[10] and advanced breast cancer.[6] Cyclophosphamide may depress B-cell proliferation, and its administration with BCG vaccine may produce increased numbers of T cells with antitumor activity.[15,18] Consecutive responding patients were given the VMCP-BCG combination, and their survival was compared with almost identical patient groups in an immediately preceding study.[3] The survival of patients receiving the VMCP-BCG program was not significantly superior to that of responders

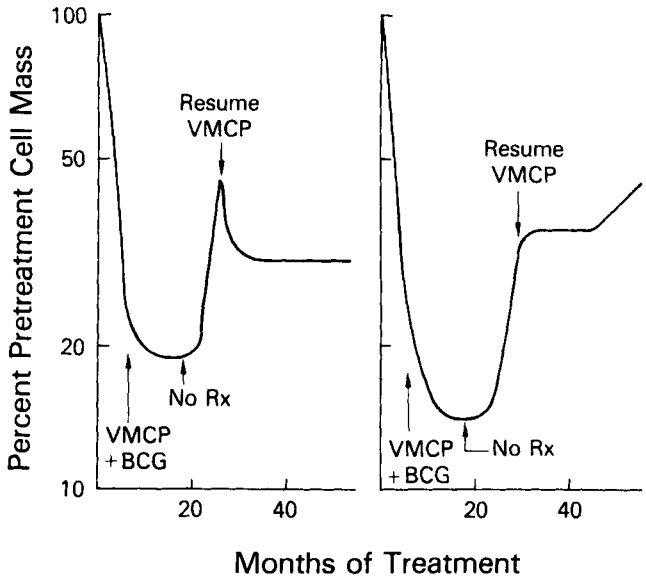

FIG. 2. Tumor mass curves in two typical patients relapsing from unmaintained remissions. While the resumption of VMCP did not achieve a 50% reduction in cell mass, and the patients were considered unresponsive, prolonged tumor mass stability continued for more than two years.

maintained on previous SWOG treatments or on no treatment. Thus, these results did not support a useful role for BCG immunotherapy in patients with myeloma, although further evaluations may reveal a small percentage of patients with very long survival. These negative results may have been because of the preserved cell-mediated immunity in patients with multiple myeloma, so that any further enhancement with BCG, as occurred in patients with acute leukemia or melanoma,[9,10] was less likely to develop. On the other hand, several groups have reported a survival benefit for BCG in patients with non-Hodgkin's lymphoma,[11,13] another B-cell neoplasm derived from cells similar to plasma cells in the differentiation pathway.[17] For patients with nodular lymphoma, the benefit from BCG was observed only when this immunostimulant was added during induction and not during maintenance.[13] This suggested that a similar strategy may be useful in myeloma patients.

TABLE 5. Pretreatment Skin Test Reactions to Various Antigens (Median Values for Mean Diameter of Induration)

	No. patients	Dermatophytin	Varidase	Candida	Mumps	PPD	KLH
Normal volunteers* (40–80 years old)	131	8	7	16	18	1	†
Multiple myeloma							
All patients	42	10	10	18	20	5	5
High tumor mass	12	9	10	21	24	5	4
Responsive	21	11	10	18	19	7	5
Three year survival	21‡	13	12	18	20	7	6

* Reference 16.
† Data not available.
‡ Includes 17 responsive and four unresponsive patients.

In comparison with normal subjects of comparable age, myeloma patients showed no impairment of delayed hypersensitivity as measured by their reaction to a battery of skin tests. These findings emphasized the importance of making comparisons with an older age control population. In this first study reported of serial measurement of skin tests in myeloma, no correlations were noted between the intensity of the reaction to recall antigens and the likelihood of a response to treatment or the survival time. This contrasts with similar studies in acute leukemia, breast cancer, and melanoma in which the reaction to some skin tests appeared to predict the response to chemotherapy.[6,9,10] Pretreatment and serial skin testing with the antigens available may have provided an insensitive technique for assessing immunity in patients with multiple myeloma.

The duration of unmaintained remission, as defined by the duration of low and constant myeloma protein values, was evaluated in 69 patients who had completed the chemoimmunotherapy program with at least 18 months of total therapy. The unmaintained remission time of nine months for all patients was similar to that found in patients followed on no treatment after only 12 months of initial treatment.[2] Early relapse usually occurred after withholding treatment in all patients with persistent serum peaks; chemotherapy should probably be continued in such patients to prevent disease morbidity. The disappearance of myeloma protein that was compatible with a marked tumor reduction was usually associated with a long unmaintained remission time, and this was most apparent in patients with a low pretreatment tumor mass in whom serum peaks had disappeared. Myeloma relapse was undoubtedly developing in most patients before the reappearance of myeloma proteins on the electrophoretic strip, but only rarely did any disease morbidity develop before chemotherapy was resumed. In view of the long duration of disease stability in most of these patients and the lack of curative treatment, it seems reasonable to withhold treatment until electrophoretic or radiographic evidence of relapse becomes apparent.

Previous analyses had suggested that a subclone of cells that was still sensitive to alkylating agent-prednisone treatment usually accounted for the initial relapse in patients who had responded and were then followed without chemotherapy.[12] Thus, while second remissions developed in about three fourths of the patients who had relapsed after 12 months of initial therapy,[2] recontrol occurred in only one half of the patients who received 18 months of treatment. While the true frequency of recontrol may be intermediate between these figures (namely about 60%), one wonders whether the longer duration of initial therapy provided more effective control of the sensitive tumor subclone and the more likely emergence of subclones resistant to the drugs given.[12] In fact, the persistence of any myeloma protein at the end of the remission maintenance phase must have reflected the presence of resistant cells even before the unmaintained remission phase began. Thus, resistance to individual drugs may develop early after the start of treatment but may be expressed slowly in accordance with the growth of resistant cells. In that case, the value of any specific maintenance treatment has less relevance than the prevention of tumor resistance to the drugs now available. Treatment regimens that include all effective drugs from the start, such as in current SWOG alternating and sequential drug combinations, may clarify this question.

The increasing tumor resistance with time is consistent with previous analyses indicating that resistant cells constitute most of the myeloma cell population after two years of treatment.[2,12] One would then expect tumor recontrol in almost all patients relapsing on no treatment after a short period of initial treatment, and drug resistance after several years of chemotherapy. Perhaps, the "ideal patient" to follow without treatment is one in whom the serum myeloma protein disappeared early so that follow-up without therapy could commence between 6–12 months. While these patients might be assured of second remissions with retreatment for relapse, the unmaintained remission time might be short because of the high number of residual plasma cells.[2] Conversely, longer durations of consolidation treatment may be followed by longer unmaintained remissions, but the frequency of tumor recontrol would be less as noted here. With either approach, a good quality survival of at least one year from the resumption of treatment should be anticipated, since either second remissions or a prolonged stable mass will ensue in most patients.

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