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Treatment of Multiple Myeloma with M-2 Protocol and without Maintenance Therapy

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Abstract—*From September 1975 to December 1981, 63 consecutive untreated patients with multiple myeloma received the Lee M-2 protocol. We used the same drugs (melphalan, cyclophosphamide, vincristine, BCNU and prednisone) but employed the lowest suggested doses and recycled earlier, i.e. after 21–28 days. Thirty-five patients (62.5%) were in stage III, 16 (28.6%) in stage II and 5 (8.9%) in stage I. An objective response (reduction in paraprotein production rate >50%) was obtained in 44 out of 56 cases (78%); 32 (57%) had a reduction >75%. The median duration of response was 21.5 months. In responding patients the treatment was stopped after 1 yr and resumed only at relapse. Twenty-two out of 25 retreated patients are now evaluable. Eighteen of them (82%) responded again; in retreatment the degree of response was lower, but the duration of second response was only slightly lower than the first response (15.7 vs 21.5 months, NS). Of 7 patients receiving a third M-2 reinduction 4 responded again. The median survival for all the patients is 51 months. The high rate of second response to the M-2 regimen after an unmaintained remission brings into question the value of continuous therapy in responsive multiple myeloma.*

INTRODUCTION

STANDARD treatment of multiple myeloma with melphalan and prednisone produced objective responses in about 30–50% of patients and a median survival for all patients of approximately 24 months [1, 2]. Responses have also been obtained with cyclophosphamide [3, 4], BCNU [5], procarbazine [6] and adriamycin [7]. Vincristine, although not effective in the initial treatment of myeloma, has shown activity in further reducing the tumor cell mass once the 'plateau phase' has been reached with other drugs [8]. More recently vindesine has also shown some activity during active disease [9].

There is still a controversy about whether combinations of agents are associated with longer duration of remission and survival [10–12]. Case *et al.* and Lee *et al.*, using a combination of cytotoxic drugs consisting of melphalan, prednisone, cyclophosphamide, vincristine and BCNU (M-2 protocol), obtained a very high response rate (87%) and a median survival of 50 months [13, 14].

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We report here the results of a study on 56 patients treated between 1975 and 1981 with the same regimen and a slightly different policy: we used the same drugs with the lowest suggested doses, but recycled earlier, i.e. after 3–4 weeks; in responding patients treatment was stopped after 1 yr [15, 16].

MATERIALS AND METHODS

Patients

Between September 1975 and December 1981, 63 consecutive patients with plasma cell myeloma were included in this study. Until now 56 patients have been followed for a long enough period to permit the evaluation of response and survival. No patient had received prior chemotherapy; patients who had received only localized radiotherapy were eligible.

Diagnosis was established according to the criteria of the Chronic Leukemia–Myeloma Task Force guidelines [17]; the patients were clinically staged using the system developed by Durie and Salmon [18]. The total body burden of myeloma cells was derived from the general formulas of Salmon and Wampler [19].

Of the 56 evaluable patients, 35 (62.5%) were in stage III, 16 (28.6%) in stage II and 5 (8.9%) in stage I. Twelve out of 56 (21.4%) were subclassified B on the basis of renal function (BUN >30 mg/dl). Six patients (10.7%) had pure Bence Jones myeloma and 3 (5%) had no identifiable paraprotein in either serum or urine. One patient had IgM myeloma with bone lysis [20–22]. The clinical characteristics of the patients and the myeloma protein type are presented in Tables 1 and 2.

Table 1. Clinical characteristics of the patients

	No. of patients
Median age: 61 yr (range: 32–76 yr)	
Sex:	
males	38
females	18
Median performance status (PS) (Karnofsky scale):70	
PS: 50–70	23
PS: >70	33
BUN >30 mg/dl	12
Serum uric acid >8 mg/dl	17
Serum calcium >12 mg/dl	5
Haemoglobin <10 g/dl	13
Lytic bone lesions (on skeletal X-rays)	47

*Table 2. Paraprotein excretion**

	No. of patients
IgG	35
IgA	9
IgD	2
IgM	1
κ light chains	4
λ light chains	2
No identifiable paraprotein	3

*Overall 31 patients had κ and 9 had λ subtypes of immunoglobulin.

Treatment

The treatment was usually administered on an outpatient basis. All patients were given the M-2 protocol according to Lee *et al.* and Case *et al.* [13, 14], with BCNU 0.5–1 mg/kg i.v. on day 1, cyclophosphamide 10 mg/kg i.v. on day 1, melphalan 0.1–0.25 mg/kg p.o. on days 1–4, vincristine 1 mg i.v. (on day 21 until December 1979 [14] and later on day 1 [13]) and prednisone 1 mg/kg p.o. on days 1–5. Initially the cycle was restarted on day 29; after December 1979, if blood cell counts had reverted to normal values, the cycle was restarted on day 22: in this case the lowest proposed doses were administered. In responding patients chemotherapy was stopped after 1 yr. At relapse therapy was resumed; if a second remission was attained, therapy was stopped again after 5–10 months, depending on the bone marrow toxicity and the reaching of a new stable plateau in the M serum component.

Evaluation

Myeloma cell mass changes were calculated from changes in serum myeloma paraprotein production rate using a computerized system developed by Salmon and Wampler [19]. Plasma volume was obtained initially and at least every 6 months with the 131-albumin method. When a direct determination was not available during the course of treatment, plasma volume was estimated from body weight and hematocrit according to the formula described by Nadler *et al.* [23]. Calculations of the myeloma cell mass were performed at staging and after at least every 2 courses of therapy. After stopping treatment, calculations were made at least every 3 months.

An objective response was defined as a reduction of 50% or more of the paraprotein production rate and of urinary Bence Jones protein; duration of response was calculated from this point. Relapse was defined as an increase of more than 25% from the lowest value obtained. Improvement in, or maintenance of, blood hemoglobin concentration above 9.0 g/dl, serum albumin above 3.0 g/dl and calcium level below 12 mg/dl were necessary requirements for a response to be accepted. Second remission was defined as a reduction of more than 25% in the serum myeloma protein production rate at the time of relapse, the reduction reaching a level lower than 50% of the initial M-component value.

Statistical analysis

For the comparison of two proportions, the χ square test, corrected according to Yates, was applied to the result of a 2×2 table [24]; for the comparison of two means Student's t test was used. Survival curves were calculated from the start of therapy by the Kaplan–Meier product limit method [25]; for comparison of curves the log-rank test was applied [26]. All reported P values refer to two-tailed tests.

RESULTS

Response to treatment

An objective response was obtained in 44 out of 56 patients (78%); 32 (57%) had an objective response of more than 75% and 12 (21.5%) had an objective response between 50 and 75% (Table 3). In another 6 patients there was a reduction of the paraprotein production rate of less than 50%; only in 6 patients was there a progression of disease from the beginning.

Table 3. Evaluation of response: distribution of the patients according to stage and degree of response

Stage	No. of patients	Response >75% No. of patients	(%)	75–50% No. of patients	(%)	<50% No. of patients	(%)
III	35	22	(66)	8	(20)	5	(14)
II	16	9	(56)	2	(13)	5	(31)
I	5	4		2		2	
Total	56	32		12		12	

There was no statistically significant difference in response rate between patients secreting immunoglobulins IgG or IgA; 5 out of 6 with only light chains responded and 3 out of 4 without detectable secretion had clinical evidence of response. The responses were also equally distributed in all 3 stages. The maximum response was obtained on average after 5 courses of therapy, but in 3 cases the maximum response was obtained only after 10 courses.

The mean duration of response was 21.5 months (range, 5–64 months; median, 18 months). The difference in mean duration of response between stage III patients (18 months) and stage I and II patients (29 months) was not statistically significant. However, the duration of the unmaintained remission (computed from the last course of chemotherapy) differed significantly: patients in stages I and II had a mean duration of unmaintained remission of more than 2 yr, while the corresponding value for stage III patients was less than 1 yr ($P < 0.05$) (Table 4).

In stage III patients the duration of response is clearly linked to the reduction of the paraprotein production rate (20 months with a response >75%, 8 months with a response between 50 and 75%; $P < 0.05$), although this does not occur in stage I and II patients (NS).

Two responding patients underwent relapse while still under M-2 treatment and they both died soon after.

Table 4. Mean duration of response (in months) by stages

	Stage III	Stage I + II	*P*
Overall duration of response*	18	29	NS
Duration of unmaintained remission†	11,4	24,6	<0.05

*Computed from the attainment of 50% reduction of paraprotein production rate.
†Computed from the interruption of treatment.

At relapse the M-2 protocol was resumed, and 22 out of 25 retreated patients were evaluable: 18 out of the 22 (82%) responded again, but only 6 (27%) had an objective response of more than 75% while 12 (55%) had an objective response between 50 and 75%.

The overall response was similar in induction or in reinduction (78 vs 82%), but in retreatment the degree of response was lower ($P < 0.01$) (Table 5). Also, the duration of the second response was slighly lower than the first response (15.7 vs 21.5 months; NS).

Survival

The median duration of survival was 51 months (Fig. 1). Survival duration varied according to the clinical stage of the patients: stage I patients lived longer than stage II patients ($P < 0.001$), and stage

Table 5. Degree and duration of response to chemotherapy in induction and in retreatment

	Response >75% No. of patients	(%)	50–75% No. of patients	(%)	Overall No. of patients	(%)	Duration of reponse (months)
Induction therapy (56 patients)	32	(57)	12	(21)	44	(78)	21.5
Retreatment (22 patients)	6	(27)	12	(55)	18	(82)	15.7

The number of patients having a response >75% is higher in induction than in retreatment ($P < 0.05$), but the overall response durations do not differ significantly.

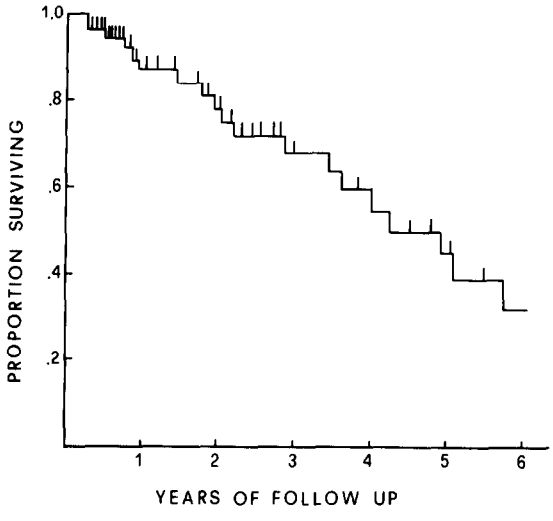

Fig. 1. Overall survival from start of therapy.

II patients in turn lived longer than stage III patients ($P < 0.05$), while the difference between subgroups A and B was not significant.

There was a clear difference in survival between patients with a response to therapy equal to or more than 50% and those with a response of less than 50%: the former had a median survival of 63.5 months, the latter of 8 months ($P < 0.01$) (Fig. 2). If we further distinguish between patients who progressed and those who had a decrease of less than 50%, we can see that for the former survival was very short (2, 3, 4, 5, 8, 8+ months), while for the latter survival may last as long as in 'responders' (3+, 9+, 9, 41, 56, 63 months). Until now 20 patients have died, 7 of them in the first year.

Toxicity

The regimen was administered on an outpatient basis and was generally well tolerated. Gastrointestinal toxicity and myelosuppression were the most prominent side-effects. Nausea and vomiting, associated with BCNU and cyclophosphamide, were occasionally noted. Hematological toxicity often occurred, but generally it was not prominent. For the first 37 patients the courses of treatment were administered every 28 days. As the M-2 protocol provides a certain range of dosage for BCNU and melphalan, these patients received the higher proposed doses. For leukopenia (<3500 leukocytes/μl) and/or thrombocytopenia (<100,000 platelets/μl) it was necessary to reduce the doses in 18% of such cycles and to delay the initiation of following courses in 30%.

In 19 of 56 patients the courses were administered at three-week intervals. For these patients the administered drugs were in the lower range of the M-2 regimen. In 10% of such courses the initial dose was further reduced for leukopenia and/or thrombocytopenia, and in 33% it was necessary to delay the subsequent courses (on average for 1 week).

In all but two patients the course was delayed at least once during the planned 1-yr treatment period, but generally leukopenia and/or thrombocytopenia were moderate.

With the three-week intervals, 7 out of 19 patients reached a white count between 2500 and 1800/μl and 6 out of 19 had a platelet count between 50,000 and 70,000/μl, both evaluated on the day of the subsequent drug injection.

There was one possible drug-related death: a non-responding patient developed granulocytopenia and pneumococcal pneumonia after 2 courses of therapy. A severe leukopenia was observed in another patient: at diagnosis he had 2800 leukocytes/μl and after 2 courses (with reduced dose) he had developed a prolonged leukopenia (1100 leukocytes/μl) which lasted for 5 months.

Prednisone was omitted in one patient with duodenal ulcer and reduced in two other patients. To all the other patients prednisone was given at the full dosage for 5 days, without any important side-effects. Paresthesias due to vincristine occurred frequently, but we never observed severe neurotoxicity.

To date we have observed no case of acute monomyelocytic leukemia among our patients.

DISCUSSION

Without effective chemotherapy, the median survival of patients with multiple myeloma is less than 1 yr from diagnosis. In the last 2 decades many reports have suggested that melphalan or cyclophosphamide, either as single agents or combined with prednisone, could obtain objective responses in 30–50% of patients, with a median survival of 24 months. More recently numerous attempts have been made to improve upon these results. Controversy continues as to whether or not combination chemotherapy is clearly superior to 'standard' therapy with melphalan and prednisone (MP). Cohen *et al.* [27], using a combination of BCNU, cyclophosphamide and prednisone, found no apparent advantage over MP: this study was not randomized and the combination chemotherapy did not contain melphalan.

Harley *et al.* [28], in a prospective randomized trial comparing a regimen of three intravenous alkylating agents, i.e. melphalan plus cyclophosphamide plus BCNU associated with prednisone (BCMP), against a regimen employing oral melphalan associated with prednisone,

found that BCMP significantly improved the response rate over that obtained with MP alone but did not improve the overall survival of patients. However, poor-prognosis stage III patients treated with BCMP survived longer than those treated with MP.

The Canadian Cooperative Study Group [29], comparing in a prospective study MP with BCMP given in alternating or concurrent schedules, obtained no advantage for the BCMP combination. However, a very high proportion of patients were in stages I and II and it may be difficult to show the benefit of combination chemotherapy in stages I and II of the disease.

The Southwest Oncology Group (SWOG) studied a variety of combinations by the addition to MP of cyclophosphamide, procarbazine, adriamycin, procarbazine plus vincristine, cyclophosphamide plus BCNU or vincristine and cyclophosphamide (VMCP), or by the addition to prednisone of vincristine-cyclophosphamide-adriamycin, vincristine-BCNU-adriamycin (VBAP) or others [30, 31]. In these studies it can be seen that there is a trend towards improvement both in remission rate and in median survival from initial therapy, particularly for the regimens containing vincristine with a 3-week schedule of administration. In a more recent SWOG study, using the alternating combination of VMCP and VBAP, there is a median survival of 38 months, statistically superior to MP [32].

In 1974 Lee *et al.* made an initial report on a 5-drug protocol combining melphalan, prednisone, cyclophosphamide, BCNU and vincristine (M-2 protocol), and obtained a very high percentage of responders. In a recent paper [10] Lee *et al.*, in a group of 81 previously untreated patients, reported a response rate of 78% and a median survival from diagnosis of 48 months. In 1975 we began to treat myeloma patients with the same combination as Lee *et al.*, but with a lower dosage of drugs administered more frequently (on the average every 3–4 weeks), as compared to 5–6 weeks for Lee's protocol. The treatment was well tolerated, even when administered as frequently as every 3 weeks. The obtained response rate of 78% is comparable to that of Lee *et al.*, as is the composition of our patients (high risk vs low risk, prevalence of stage III vs stages I and II).

Whether or not to employ continued chemotherapy as maintenance treatment seems an open question. The most relevant data published by Alexanian *et al.* have shown no benefit from maintenance therapy [31, 33, 34]. It has been shown recently that during the plateau phase mitotic activity and the labeling index are low [35]. It is conceivable that treatment is not active during this phase and may even impair the response to chemotherapy at the time of relapse: prolonged exposure to the drugs can induce resistance in the residual tumor cells. In fact, in these conditions, with the exception of a few reports [13, 16], the treatment of relapsing patients has in general been disappointing [24, 37–39].

We adopted the policy of stopping treatment after 1 yr in responding patients and of resuming it at relapse. Eighty-two percent of the relapsing patients responded to retreatment: only 27% had a regression of more than 75%, as compared with 57% obtained during induction. The remission duration of the second response, however, was only slightly shorter than after the first treatment (15.7–21.5 months). It may be appropriate to compare this finding with those of Alexanian *et al.*: they reported that a second remission was obtained with MP in 16 out of 20 (80%) patients who had been treated for a limited period of 12 months with MP-containing regimens and then followed without treatment until relapse [40]. In a subsequent study [34] a second remission occurred in only 10 out of 20 (50%) patients who had been initially treated for 18 months. The overall duration of response was similar in both studies: it would seem that longer duration of initial treatment is not followed by a longer remission and can reduce the probability of obtaining a second remission at relapse.

As suggested by Hokanson *et al.* [41], a subclone of cells that are still sensitive to alkylating agents and prednisone may account for at least the first relapse in patients recurring while they are off treatment.

To achieve a prolonged unmaintained remission it seems important to obtain a good response (>75%), particularly in stage III patients, since a high number of residual myeloma cells can induce an early relapse. In our study the M-2 protocol, repeated at 3- to 4-week intervals, produced a high number of good responses (>75%); in this condition most of the patients obtained a stable plateau and a new control of disease at relapse. Even with an initial response between 75 and 50%, the interruption of therapy after 1 yr can be justified if a plateau is evident; even though the unmaintained remission is shorter, a second remission is possible and survival may be as long as with continuous therapy.

The median survival observed in our patients was 51 months. There is a clear difference in median survival time between responders and non-responders: in the latter the median survival was only 8 months. It is worth noting that in 4 out of 6 of our patients that were classified as non-responders because of a paraprotein decrease of

less than 50%, survival was as long as in responders. As other authors [13, 42] have pointed out, it is possible that a percentage of patients normally classified as 'non-responders' may in fact have a prolonged survival because of 'non-progressing disease' that is usually defined as a 'minimal cell kill'.

There is no control group in our study, but the response rate and the survival times seem promising. The major benefits to our patients may have come from the use of combination chemotherapy with alkylating agents plus vincristine and prednisone, from giving the drugs frequently (every 3–4 weeks), from not employing continuous therapy during the plateau phase and from the high number of second remissions obtained with the same drugs as those that have been used in induction. Which single feature or combination of features is more relevant to the long survival and low incidence of second tumors (no case of acute leukemia has been observed to date) needs to be clarified with randomized clinical studies.

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