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Intermittent High-dose Melphalan/Prednisone vs Continuous Low-dose Melphalan Treatment in Multiple Myeloma*

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Abstract—*Patients with newly diagnosed multiple myeloma were randomly allotted to an intermittent high-dose melphalan/prednisone (MP) treatment (120 patients) or a continuous low-dose melphalan (M) regimen (99 patients). The median observation time was* 59 months *(range 33–84). Response to therapy was obtained in* 45% *of the MP group and* 31% *of the M group (*$P < 0.05$*). No significant difference in response with regard to clinical stage was noted. Median survival was* 36 months *in the MP group and* 29 months *in the M group. Survival was longer in stage I and II myeloma than in the stage III cases, at least in the MP group. The median and* 5*-yr survival rates in stages I and II were significantly better in the MP than in the M group. Response to therapy was associated with length of survival, median survival being* 62 months *in responding patients and* 20 months *in non-responders. The MP and M groups did not differ in this respect.*

INTRODUCTION

MELPHALAN is an effective drug in the management of multiple myeloma. Singly or combined with prednisone, melphalan gives objective tumour regression and relief of bone pain and prolongs survival [1–7]. Continuous low-dose melphalan as a single-drug regimen has long been used as primary treatment in myeloma [6].

A report on intermittent high-dose melphalan, alone or in combination with prednisone (4-day courses every 6th week) was published in 1969 [1]. According to the criteria proposed by the Chronic Leukemia–Myeloma Task Force [8], the response rate was 73% with the combined drugs and 35% with the single drug. A tendency to longer median survival was also observed when the combined regimen was used. The results were subsequently supported by a similar study [9].

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The treatment schedule mainly used in Sweden at the time of these studies was continuous melphalan—a loading dose followed by low-dose maintenance [6, 7]. As a result of the reports, a study was undertaken to compare that regimen with combined intermittent high-dose melphalan/prednisone. The study was begun in 1974 and closed in June 1978. It was designed as a prospective multicenter trial. The present report concerns 219 patients with median observation time 59 months.

MATERIALS AND METHODS

Study population and randomization

Seven hospitals participated in the trial. All newly diagnosed, untreated patients who fulfilled the diagnostic criteria for multiple myeloma (see below) and were admitted to the participating hospitals between 1 April 1974 and 30 June 1978 were considered for the study. There was no age limit. Patients who were receiving cytostatic drugs or irradiation were excluded, as were those with other, concomitant malignancies. An initial

platelet count below $100 \times 10^9/l$ also caused exclusion (6 cases). No other patients were excluded.

Patients accepted for the study were randomized to treatment with intermittent melphalan/prednisone (MP) or continuous melphalan (M) (see below). Of the 229 patients initially accepted for the study, 10 (6 in MP and 4 in M group) were rejected because of inadequate initial documentation. Of the remaining 219 patients, 120 were allotted to the MP group and 99 to the M group. Patients born on even dates received MP treatment and those born on uneven dates M therapy. This procedure generally creates groups of equal magnitude, but differences may occur. In this study the allocation was somewhat unequal. However, the numerical difference between the groups was not statistically significant and was of random causation. Moreover, a check-up in the central diagnosis register showed that all newly diagnosed patients with multiple myeloma within the referring area of the hospitals were included. No intergroup transferrings were made.

Clinical evaluation

The diagnosis of multiple myeloma was established when at least two of the following criteria [5] were met: (1) a monoclonal immunoglobulin peak revealed at electrophoresis of serum and/or urine, together with a subnormal concentration of at least one non-monoclonal immunoglobulin class (IgG, IgM, IgA) in serum; (2) more than 10% plasma cells in the bone marrow; (3) osteolytic and/or osteoporotic bone lesions compatible with multiple myeloma.

The following laboratory tests were performed at the time of diagnosis: agarose electrophoresis of serum and of ×100 concentrated urine; determination of the isotype of the monoclonal immunoglobulin by immunoelectrophoresis or immune fixation method; measurement of IgG, IgM and IgA (in 1 case also IgD) concentrations by Mancini *et al.*'s method [10] or by rocket electrophoresis according to Laurell [11]; quantification of 24-hr urinary protein with Biuret technique [12].

Roentgenographic studies were made of the skull, vertebral column and pelvic bones. A bone-marrow specimen was obtained by aspiration biopsy, usually from the sternum. The percentage of plasma cells was determined by counting at least 500 cells in separate view fields of stained smears from bone-marrow aspirates.

The initial evaluation also included the following measurements: erythrocyte sedimentation rate (ESR), hemoglobin concentration, total and differential white blood count (WBC), platelet and reticulocyte counts, and serum levels of albumin, calcium, creatinine, uric acid and liver enzymes. In all but two of the patients the disease was clinically staged according to the system proposed by Durie and Salmon [13]. The exceptions were a patient with IgD myeloma and one with non-secretory myeloma.

Treatment schedules

The MP patients were given 0.25 mg melphalan/kg body wt/day and 2 mg prednisone/kg body wt/day by mouth during four consecutive days, usually without tapering of prednisone. The course was repeated every 6th week. Treatment was deferred or reduced if the neutrophil count was below $2 \times 10^9/l$ and/or the platelet count below $100 \times 10^9/l$. The prednisone dosage was reduced only if side-effects could be attributed to the steroid component. The M patients received a loading dose of 0.07 mg melphalan/kg body wt/day for a maximum of three weeks. After a drug-free interval of one to two weeks, a daily dose of melphalan was instituted. The dose was adjusted to keep WBCs around $2 \times 10^9/l$ and/or platelet count around $100 \times 10^9/l$: it was usually between 1 and 2 mg. In both groups therapy was continued until the disease progressed.

Local radiotherapy (*ca.* 30 Gy) was allowed for relief of pain. Hypercalcemia was treated with hydration and furosemide and, if clinically indicated, also prednisone until normalization of the serum calcium level. Blood transfusions and analgesics were given as required. Spinal cord compression with neurological manifestations was usually treated with surgical decompression within 36 hr.

Follow-up

Clinical examination and blood-cell counts were repeated according to individual requirements. Every 6 months, or more frequently if clinically indicated, the following laboratory observations were made: ESR, hemoglobin concentration, total and differential WBC, platelet and reticulocyte counts, serum levels of albumin, calcium and creatinine, electrophoresis of serum and urine, measurements of serum IgG, IgM and IgA and of 24-hr urinary protein excretion, and differential counts of bone-marrow smears. Skeletal roentgenographs were taken when clinically indicated.

Criteria of response to treatment

Clinical response was defined mainly according to the criteria proposed by the Committee of the Chronic Leukemia–Myeloma Task Force [8]. These were primarily: (1) decrease of serum M component concentration by more than 50% of

the pretreatment value; (2) decrease of urinary light-chain excretion to less than 0.2 g/24 hr; and (3) more than 50% decrease of the plasmocytoma size. In addition, patients were classified as responders only if the hemoglobin level was ⩾90 g/l, serum albumin ⩾30 g/l and serum calcium <2.61 mmol/l. In the patient with non-secretory myeloma, numerical reduction of bone-marrow plasma cells to ⩽10% was substituted for criteria 1 and 2.

Statistical methods

Differences in relative numbers were tested with the chi-square test. Survival curves were plotted according to the life-table method [14]. The significance of intergroup differences in regard to expected survival was assessed with the log-rank test [15].

RESULTS

The distribution of age and clinical stage of multiple myeloma was similar in the two treatment groups [Fig. 1(a and b), Table 1]. The mean age was 68 yr in the MP group and 67 yr in the M group. No statistically significant inter-group difference was found at the initial examination with regard to hemoglobin, serum levels of albumin, calcium or creatinine, or immunoglobulin class. The serum creatinine was ⩾200 μmol/l in 30 patients, 25 of whom were in clinical stage III.

A follow-up study was performed in March 1981. The median observation time in both groups then was 59 months (range 33–84 months). The total survival time, as evaluated with life-table analysis, did not differ significantly between the two treatment groups (Fig. 2). The median survival time was 36 months in the MP group and 29 months in the M group ($P > 0.05$). The respective survival rates after 1 yr were 82 and 75%, and after 5 yr 35 and 24% ($P > 0.05$).

The graphs of patient survival were compared with figures for a general population, matched for age and sex distribution and residing in the same geographic area as the patients (Fig. 2). The mortality of the reference population was similar for both treatment groups. The mean probability of 5-yr survival in the matched controls was about 80%.

Survival in relation to clinical stage of multiple myeloma is illustrated in Fig. 3. Since each treatment group contained only 14 stage I cases, and their survival did not differ from that in stage II within the group (data not shown), stages I and

Table 1. Pre-treatment characteristics of patients with multiple myeloma

		MP group ($n = 120$)	M group ($n = 99$)
Stage of multiple myeloma			
	I	14 (12%)	14 (14%)
	II	49 (41%)	34 (34%)
	III	56 (47%)	50 (52%)
Patient age*			
all patients		68 ± 10	67 ± 11
stage	I	70 ± 10	66 ± 11
stage	II	68 ± 9	67 ± 12
stage	III	67 ± 11	66 ± 11
Sex, male/female		52/68	53/46
Hemoglobin, g/l*		111 ± 21	113 ± 24
Serum albumin, g/l*		36 ± 6	36 ± 6
Serum calcium, mmol/l*		2.46 ± 0.30	2.51 ± 0.55
Serum creatinine, μmol/l*		123 ± 109†	157 ± 172‡
Serum creatinine <200 μmol/l (No. of patients)		105 (88%)	84 (85%)
M protein class			
IgG		74 (62%)	58 (59%)
IgA		25 (20%)	27 (27%)
IgD		—	1 (1%)
Bence-Jones only		20 (17%)	13 (13%)
Non-secretory		1 (1%)	—

*Mean ± S.D.
†Range 35–1006 μmol/l.
‡Range 60–1480 μmol/l.

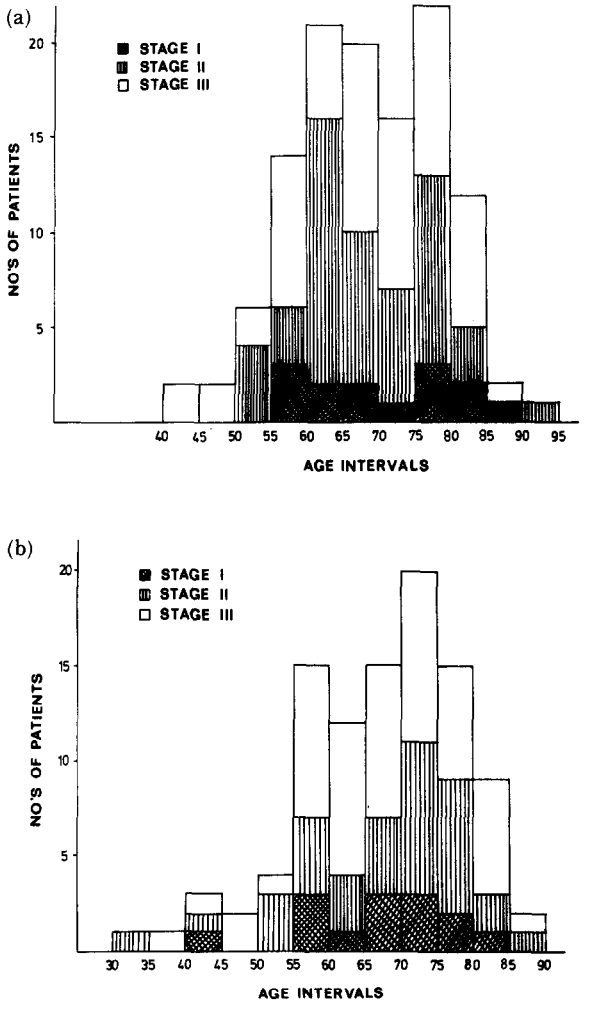

Fig. 1. Age distribution of patients in relation to clinical stage of multiple myeloma. (a) MP treatment; (b) M treatment.

II were pooled. The median survival in the pooled stages I and II was longer than in stage III in the MP group ($P < 0.005$), but not in the M group. Median and 5-yr survival in the pooled stages I and II were better in the MP than in the M group ($P < 0.001$ and $P < 0.05$ respectively). The total survival of stages I and II patients in the MP group, however, was not significantly better ($P = 0.07$) than for M patients in corresponding stages. Survival in stage III was similar in both treatment groups (Fig. 3).

Response to primary treatment could be evaluated in 110 patients in the MP group (92%) and in 88 patients in the M group (89%). Table 2 shows that the overall rate of response was slightly higher ($P < 0.05$) in the MP than in the M group, with this tendency appearing in all clinical stages. Responding and non-responding patients were compared with regard to survival. Neither category showed any intergroup difference (Fig. 4). The median survival time was 62 months for all responders and 20 months for all non-responders ($P < 0.005$). Five-year survival was achieved in 50% of the responding patients but in only 16% of the non-responders ($P < 0.01$).

The influence of hemoglobin concentration, serum creatinine and serum calcium on survival was also analysed. In both MP and M treatment groups an initial hemoglobin value of <100 g/l was prognostically less favorable ($P < 0.05$) than >125 g/l (Fig. 5). Serum creatinine $\geqslant 120$ μmol/l was associated with poor survival rate in the MP treatment group ($P < 0.01$), but not in the M

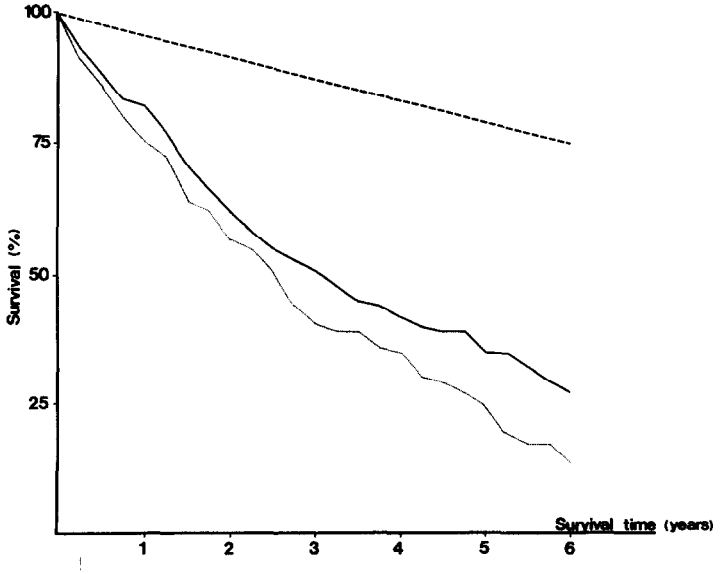

Fig. 2. Total actuarial survival time. MP therapy (——) (n = 120); M therapy (. . . .) (n = 99) (P > 0.05); (– – –) indicates survival in a matched general population.

Table 2. Clinical stage of multiple myeloma and response to treatment

Clinical stage	MP group Total patients	MP group Responders	M group Total patients	M group Responders	P-value
I	13	5 (38%)	13	4 (31%)	NS
II	47	25 (53%)	27	11 (41%)	NS
III	50	20 (40%)	48	12 (25%)	NS
Total	110	50 (45%)	88	27 (31%)	<0.05

NS = not significant.

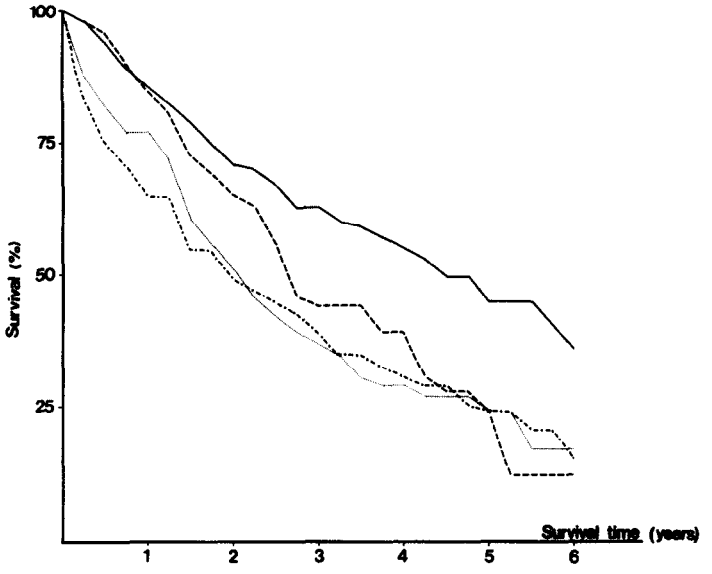

Fig. 3. Actuarial survival time in relation to clinical stage. Stage I and II MP (——) (n = 60); *stage III MP* (.....) (n = 50); *stage I and II M* (---) (n = 40); *stage III M* (-.-.-) (n = 48). *In the MP group stages I and II were associated with increased survival compared to stage III* ($P < 0.01$) *but no intergroup difference was found in the M group* ($P > 0.05$).

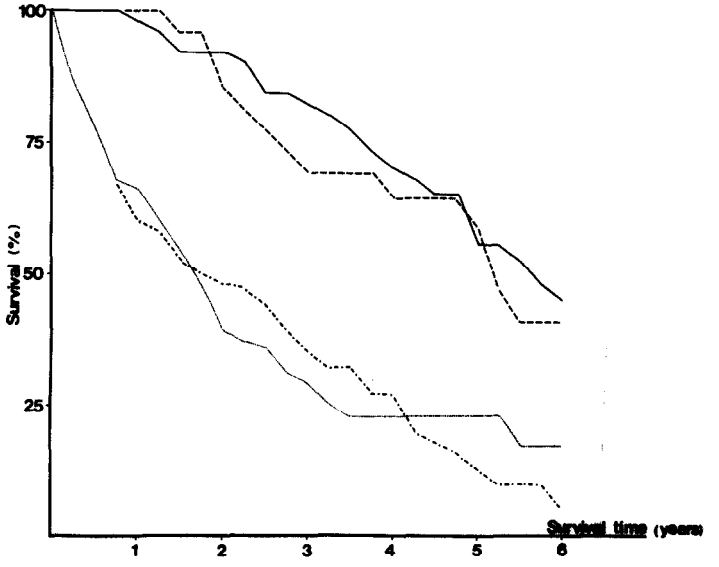

Fig. 4. Actuarial survival time in responders and non-responders. Responders to MP (——) (n = 50); *non-responders to MP* (.....) (n = 60); *responders to M* (---) (n = 27); *non-responders to M* (-.-.-.) (n = 61). *Response was associated with increased survival in both treatment groups* ($P < 0.0001$).

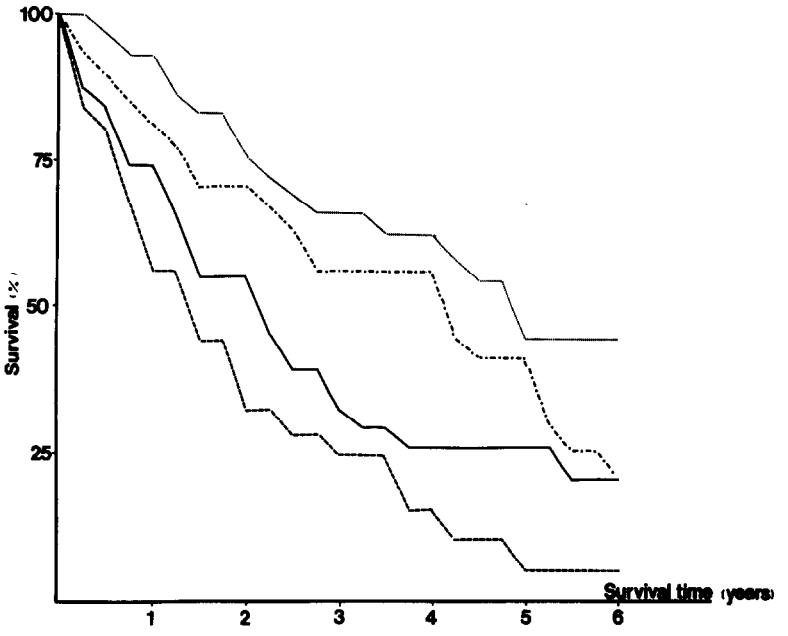

Fig. 5. Actuarial survival time in relation to initial hemoglobin concentration. Hb >125 g/l *MP* (.....) (n = 29) *and M* (-.-.-.) (n = 27); *Hb* <100 g/l *MP* (——) (n = 31) *and M* (---) (n = 25). *Hemoglobin concentration* >125 g/l *as compared to* <100 g/l *was associated with increased survival in both treatment groups* ($P < 0.05$).

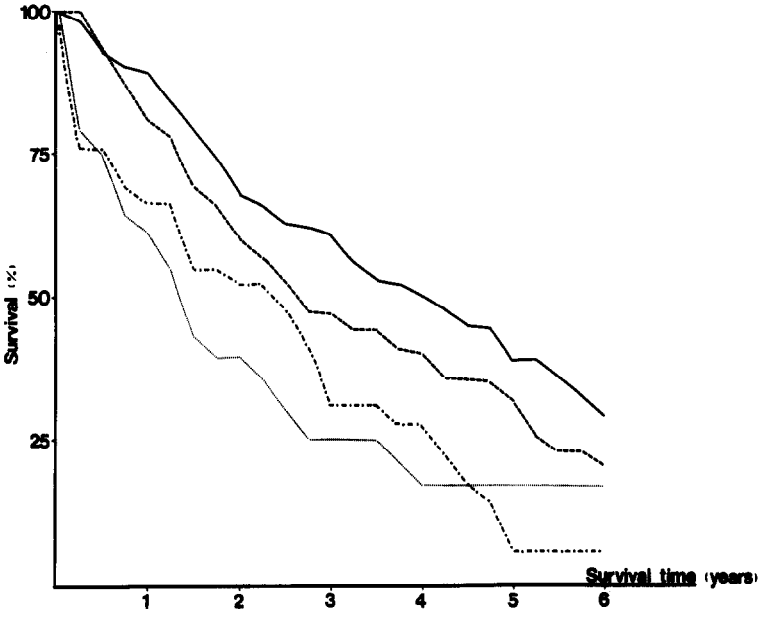

Fig. 6. Actuarial survival time in relation to initial serum creatinine level. Creatinine <120 μmol/l *MP* (——) (n = 91) *and M* (---) (n = 68). *Creatinine* ≥120 μmol/l *MP* (.....) (n = 29) *and M* (-.-.-.) (n = 31). *Serum creatinine* ≥120 μmol/l *was associated with poor survival in the MP group* ($P < 0.01$) *but not in the M group* ($P > 0.05$).

group ($P > 0.05$) (Fig. 6). Serum calcium showed no influence on survival in either group.

DISCUSSION

Continuous melphalan treatment, introduced by Waldenström [6], was the most widely used therapeutic regimen for multiple myeloma in Sweden during the 1960s and early 1970s. The study presented here was designed to compare continuous low-dose melphalan (M) with intermittent high-dose melphalan/prednisone (MP) as introduced by Alexanian *et al.* [1].

The overall median survival time was 32 months (36 months in the MP group and 29 months in the M group), which is equivalent to, or longer than, times reported in other studies

using corresponding modes of treatment [1, 4, 7, 16]. Though survival curves suggested somewhat superior results with MP than with M, the intergroup difference did not reach statistical significance. The rate of response to treatment was significantly higher in the MP group than in the M group.

The clinical staging system for multiple myeloma, as introduced by Durie and Salmon [13], has been shown to yield some prognostic information on survival [4, 16–20]. In the present study, no association was found between survival and clinical stage in the patients given melphalan only (M). In the MP group no difference in survival was found between stages I and II, but the two stages in combination were associated with a significantly longer median survival than clinical stage III. As applied in this case series, therefore, the staging system yielded limited prognostic information. Moreover, in clinical stages I and II of multiple myeloma the results as regards median and 5-yr survival rates and response to treatment seemed to be better in the MP than in the M group.

The overall response rate was 45% in the MP group and 31% in the M group. Clinical stage of the disease clearly did not influence the response to treatment. Responding patients survived longer than non-responders on average. These findings are in agreement with other reports [4, 16].

The prognosis in myeloma depends on several factors, including severity of anemia, level of serum calcium and impairment of renal function [11, 21–23; Durie, personal communication]. Analysis of these parameters in our case series confirmed the prognostic impact of anemia. Raised serum creatinine had remarkably little influence on survival in the M group but was a significant factor in the MP group. Active supportive therapy, including high fluid intake in uremic states, may have lessened the importance of this factor. No influence of serum calcium was found in either group.

From this study we conclude that, by and large, MP therapy given as intermittent high-dose courses is as effective as continuous melphalan treatment in myeloma. MP gives a higher response rate and probably longer media survival than M treatment, though the difference as regards survival was not significant in the present case series. Intermittent MP is easy to administer. The risk of bone-marrow hypoplasia is low. Side-effects of prednisone, such as diabetes, fluid retention and mental disturbance, were rare in our patients. The regimen can be followed on an outpatient basis and requires a minimum of hospital visits. M therapy, on the other hand, must be monitored with fairly frequent blood sampling in order to detect signs of bone-marrow depression, particularly during the first phase of the treatment. For these reasons the intermittent regimen seems preferable to continuous administration of melphalan.

Alexanian *et al.* [1] reported some prolongation of median survival time when prednisone was added to intermittent high-dose melphalan treatment. The Medical Research Council's Working Party on Leukemia in Adults [24], using comparable regimens, found no difference in total survival. As yet there is no convincing evidence that multiple drug chemotherapy is superior to melphalan/prednisone regimens with regard to survival, though certain subgroups of patients may benefit from more intensive programs [2, 4, 20, 22, 25, 26; Durie, personal communication]. Intermittently administered melphalan, with or without prednisone, seems to be one of the best basic regimens currently available for most patients with multiple myeloma.

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