Multiple Myeloma

PART II. THE VALUE OF MELPHALAN

D. B. BERNARD, S. R. LYNCH, T. H. BOTHWELL, W. R. BEZWODA, K. STEVENS, G. SHULMAN

SUMMARY

The results of the use of melphalan in 52 patients with multiple myeloma have been analysed. The median survival of the whole group of patients was 30 months, and of those with renal insufficiency only 12,5 months. Bence-Jones proteinuria was also a poor prognostic finding, but only because of its association with renal failure. Patients with Bence-Jones proteinuria and normal renal function had a median survival of 41 months. Responsiveness to therapy by criteria based on those of the Chronic Leukemia/Multiple Myeloma Task Force could be assessed in 25 patients. Dramatic symptomatic relief occurred in all but one of the responsive patients, but in only one-fifth of those who did not respond to therapy.

S. Afr. Med. J., **48**, 1026 (1974).

Haematology Clinic, Johannesburg General Hospital and Department of Medicine, University of the Witwatersrand, Johannesburg

D. B. BERNARD
S. R. LYNCH
T. H. BOTHWELL
W. R. BEZWODA

Departments of Chemical Pathology and Haematology, School of Pathology, South African Institute for Medical Research, and the University of the Witwatersrand, Johannesburg

K. STEVENS
G. SHULMAN

Date received: 19 December 1973.
Reprint requests to: Professor T. H. Bothwell, Medical School, Hospital Street, Johannesburg.

The value of melphalan in the treatment of multiple myeloma has been demonstrated in a number of investigations.[1,2] Symptoms are usually ameliorated, and the median survival, calculated from the time of diagnosis, is 24 months or more in patients treated with melphalan, and less than a year when the patients are untreated.[2,3] This article analyses the experience of the Haematology Clinic of Johannesburg General Hospital in using melphalan in the treatment of patients with multiple myeloma.

METHODS

The patient-population, the clinical, radiological, haematological and biochemical abnormalities recorded at the time of presentation, and the criteria used for establishing the diagnosis of multiple myeloma have been described in detail.[4]

Treatment Regimens

One of two chemotherapeutic regimens was used in each patient. Prior to 1970 melphalan was administered continuously. Seven days after an initial loading dose of 0,15 mg/kg, the patient was given between 1 and 3 mg of melphalan daily. After 1970 the regimen suggested by Alexanian and co-workers[5] was adopted. Each patient received melphalan 0,25 mg/kg/day and prednisone 2,0 mg/kg/day for 4 days. The course was repeated at intervals of approximately 6 weeks. In addition, patients receiving intermittent therapy were treated with allopurinol (100 mg every 8 hrs), beginning 48 hours before the start of chemotherapy and continuing until 3 - 4 days after the completion of the course. Patients were encouraged to take fluids liberally at this time. Additional supportive therapy, including blood transfusion, corticosteroid therapy for hypercalcaemia and radiotherapy for painful bony lesions, was given to all patients when necessary.

Response to therapy was assessed by means of criteria based upon those suggested by the Chronic Leukemia/Multiple Myeloma Task Force of the National Cancer Institute (USA).[6] A patient was considered to have responded to therapy if, after at least 3 months of therapy, there was a decrease in the concentration of the 'M'-component to less than half of the pre-treatment value, and to less than 4,0 g/100 ml; or a decrease in the level of Bence-Jones proteinuria to less than half of the pre-treatment value and to less than 0,5 g/day; and a return towards normal in the haemoglobin, serum calcium and serum albumin values where these were initially abnormal. No patient with an increase in the size or number of lytic bone lesions was considered responsive to therapy, and a patient qualified as having responded only if the criteria were sustained for 2 months or longer.

RESULTS

Twenty-one of the 52 patients treated were known to be alive at the time of writing. All patients lost to follow-up were considered dead at the last date of observation. This has been done to minimise errors in the calculation of survival results. The median survival time calculated by the life-table method was 30 months for the group as a whole (Fig. 1). The median survival for patients with IgG myeloma was 33 months. For patients with IgA myeloma it was 31 months, and for those who had Bence-Jones myeloma it was 23 months.

The effects of several factors which have been shown to influence survival in multiple myeloma were studied separately. One of the best documented is the status of renal function.[1] The median survival of all patients who had renal failure at the time of diagnosis was 12,5 months (Fig. 1). Thirteen of the 31 patients who are dead had had evidence of renal insufficiency at the time of diagnosis.

Bence-Jones proteinuria, irrespective of the presence or absence of a plasma paraprotein, was a poor prognostic feature because of its association with renal impairment. Thirty-four patients exhibited Bence-Jones proteinuria and 13 (38%) of them had renal impairment. Of the 18 patients who had no Bence-Jones proteinuria, 5 (28%) showed

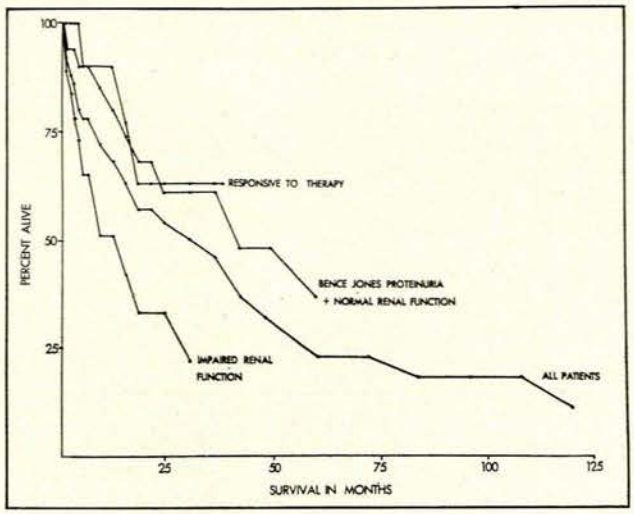

Fig. 1. Survival from time of diagnosis.

evidence of renal insufficiency. Twenty-one patients had Bence-Jones proteinuria and no evidence of impairment of renal function, and their median survival was 41 months.

The third factor considered was the patients' response to therapy. Twenty-five patients fulfilled the conditions required for evaluation by the criteria we chose. The effects of therapy on the levels of plasma paraprotein and urinary Bence-Jones protein in an unresponsive and a responsive patient are portrayed in Fig. 2. Ten patients (40%) qualified as responders and 7 of them were alive at the time of writing. It therefore appears that the median survival of the responding group will be considerably longer than that of the whole group of patients, although the exact value cannot yet be determined (Fig. 1). Of the 10 patients who responded to therapy, 9 had a dramatic improvement in their symptoms, while only 3 of the 15 non-responders experienced symptomatic relief.

Sixteen of the 25 evaluable patients had an IgG paraprotein and 7 of these responded to treatment; and 6 patients had an IgA paraprotein, of whom one responded. There were no differences between responders and non-responders in the degree of bone marrow infiltration, serum calcium concentration, serum uric-acid concentration or extent of skeletal involvement. Bone marrow depression with peripheral cytopenia (white blood cell count below 3 500/mm^3 and platelet count below 150 000/mm^3) occurred at some time during treatment in 85% of patients who responded to chemotherapy, but in only 33% of those who did not.

Six of the evaluable patients had received the continuous melphalan regimen and 19 the intermittent high-dose melphalan-prednisone regimen. All 10 patients who responded to therapy received the regimen of intermittent high-dose chemotherapy. The mean time which elapsed before the criteria of response were achieved, was 7 months. Five additional patients who are at present being treated according to this regimen show a steady fall in the 'M'-component, but are not yet evaluable since they have not yet reached 50% of the pre-treatment value.

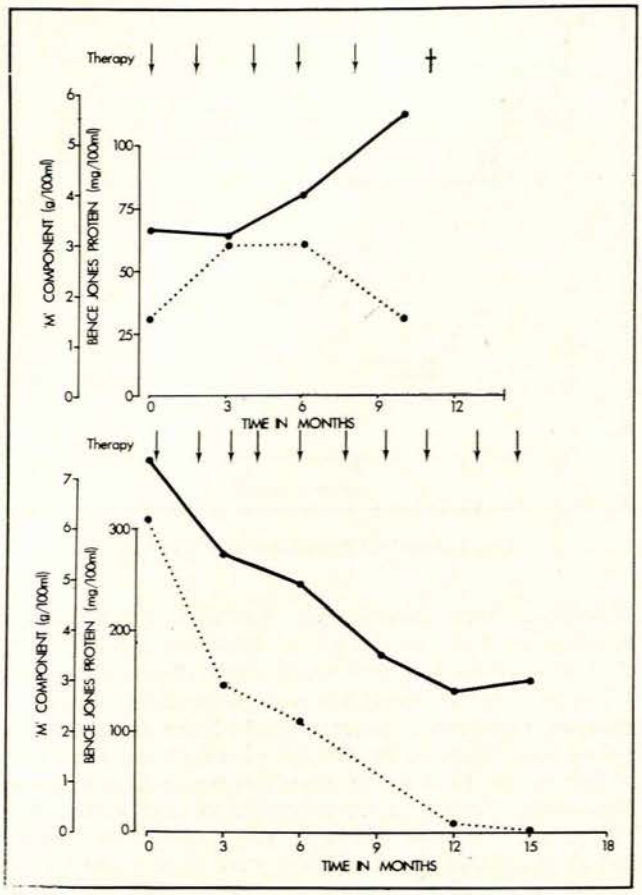

Fig. 2. The effect of the intermittent high-dose melphalan-prednisone therapeutic regimen on the 'M'-component concentration (solid line), and urinary Bence-Jones protein concentration (dotted line), in a patient who failed to respond to therapy (upper diagram), and one who responded to therapy (lower diagram). Courses of therapy are indicated by vertical arrows. The patient who failed to respond died 11 months after the commencement of therapy, while the patient who responded remains well and free of symptoms.

DISCUSSION

Renal impairment is associated with a poor prognosis in patients suffering from multiple myeloma.[1] Bence-Jones proteinuria has also been reported to be associated with a poor prognosis.[7] Our findings are, however, in keeping with those of Galton,[8] and indicate that survival is not impaired if Bence-Jones proteinuria occurs in the absence of renal failure. The poor prognosis of patients with Bence-Jones myeloma also appears to be the result of renal insufficiency. In this study 5 of the 6 patients with the condition had renal failure at the time of diagnosis.

The value of melphalan in prolonging the survival of patients with multiple myeloma is apparent. The over-all median survival of 30 months compares favourably with that reported from other centres.[1,2,5] The plasma 'M'-component provides a means of measuring the response to therapy, since it has been shown to bear a quantitative relationship to the myeloma cell mass.[9] Alexanian and co-workers[5] have demonstrated that patients whose tumours are responsive to melphalan have a median survival that is more than 2 years longer than those with unresponsive tumours. The median survival of the latter group was in fact no longer than that of untreated patients.[5] Forty per cent of the evaluable patients in the present study fulfilled the criteria of response to therapy. Other investigations have reported response rates between 15% and 85%.[2,5] In the present study the median survival of responsive patients will significantly exceed that of the group as a whole (Fig. 1). Moreover, 90% of patients who responded to therapy experienced a dramatic improvement in their symptoms, while only 20% of non-responders obtained symptomatic relief.

Although the numbers are too small for any definitive conclusions to be drawn, the present investigation supports the evidence of Alexanian and co-workers[5] regarding the superiority of an intermittent high-dose melphalan-prednisone regimen. The Acute Leukemia Group B and the Eastern Co-operative Oncology Group have also recently reported an improved response rate and a prolongation of survival in good-risk patients given a combination of melphalan and prednisone.[10] Although prednisone appears to be an important addition to the therapeutic regimen for multiple myeloma, the difference in response in our patients may be in part a reflection of inadequate melphalan dosage used in patients receiving continuous therapy. Significant leucopenia occurred in 85% of responders, but in only 33% of non-responders.

In our survey the average time taken for remission to occur in responsive patients was 7 months, although subjective improvement was usually rapid. The time taken to achieve a remission appears to be longer in our patients than it was in the group of patients reported by Alexanian and his co-workers.[11] Their experience indicated that more than half the patients who respond to therapy achieve a remission within 3 months. Johansson[12] has, however, reported a better prognosis in patients whose immunoglobulin level falls slowly than in those in whom there is a rapid fall.

We wish to thank the Director of the South African Institute for Medical Research for facilities to carry out this study, and the Medical Research Council and Atomic Energy Board for financial support.

REFERENCES

1. Report of the Medical Research Council's Working Party for Therapeutic Trials in Leukaemia (1971): Brit. Med. J., **1**, 640.
2. Bergsagel, D. E., Griffith, K. M. and Haut, A. (1967): Advanc. Cancer Res., **10**, 311.
3. Study Committee of the Midwest Co-operative Chemotherapy Group (1964): J. Amer. Med. Assoc., **188**, 741.
4. Shulman, G., Stevens, K., Bernard, D. B., Bothwell, T. H., Bezwoda, W. R. and Lynch, S. R. (1974): S. Afr. Med. J., **48**, 1023.
5. Alexanian, R., Haut, A., Khan, A. U., Lane, M., McKelvey, E. M., Migliore, P. J., Stuckey, W. J. jun. and Wilson, H. E. (1969): J. Amer. Med. Assoc., **208**, 1680.
6. Committee of the Chronic Leukemia/Multiple Myeloma Task Force of the National Cancer Institute (1968): Cancer Chemother. Rep. suppl., **1**, 17.
7. Waldenström, J. (1964): Brit. Med. J., **1**, 859.
8. Galton, D. A. G. (1971): *Ibid.*, **2**, 323.
9. Salmon, S. E. (1971): *Ibid.*, **2**, 321.
10. Costa, G., Engle, R. L., Schilling, A., Carbone, P., Kochwa, S., Nachman, R. L. and Glidewell, O. (1973): Amer. J. Med., **54**, 589.
11. Alexanian, R., Bonnet, J., Gehan, E., Haut, A., Hewlett, J., Lane, M., Monto, R. and Wilson, H. (1972): Cancer, **30**, 382.
12. Johansson, B. (1971): Brit. Med. J., **2**, 327.