

## The management of myelomatosis

A. F. BROAD  
M.B., B.S., D.M.R.T.

E. W. EMERY  
M.B., F.F.R.

J. N. GODLEE  
M.A., M.B., F.F.R.

T. A. J. PRANKERD  
M.D., F.R.C.P.

*From the Departments of Radiotherapy and Clinical Haematology,  
University College Hospital, London, W.C.1*

### Summary

Thirty-six out of sixty-two cases of myelomatosis have been treated with melphalan.

Platelet counts were used as a guide to dosage early in the course of treatment, after which a more empirical dosage (0.15 mg/kg/day) was used in 1-week courses given every 12 weeks.

Rapid deterioration and death occur in a small number of patients whatever therapy is given.

In the group treated with melphalan the median survival time was 25 months, longer than in those treated with radiotherapy or other chemotherapeutic agents.

### Introduction

Melphalan (phenylalanine mustard) is now generally accepted as a potent drug in the treatment of myelomatosis. Different authors have taken different criteria as indices of successful treatment. Waldenström (1964) for instance regards the return of serum protein anomalies to normal as an important criterion; Speed, Galton & Swan (1964), the overall symptomatic improvement, and the Acute Leukaemia Co-operative Group, an improvement in survival times.

The present report of sixty-two cases with proven myelomatosis (thirty-six of whom were treated with melphalan) aims to outline some particular problems in the management of this disease and to assess the relative survival times of those treated with melphalan against those not so treated.

Several problems emerge in the other surveys of the treatment of this disease. Firstly there is a relatively high mortality in the early months after diagnosis and the start of treatment. Secondly, there appears to be an improvement in the median survival time of patients treated with melphalan but in the great majority of cases the treated patients will die of the disease or one of

its complications. Thirdly, melphalan fails to control the disease in some cases (two cases in this series) and there may be progressive osteoporosis or anaemia indicating drug resistance or marrow failure. Fourthly, the frequent attendance of patients at a hospital for clinical assessment and haematological review presents a strain on the patient and may overtax the resources of some smaller departments.

### Material

The series consists of sixty-two cases of proved myelomatosis, the diagnoses being based on finding an excess of typical myeloma cells in the bone marrow, a monoclonal type of increase in serum globulins on electrophoresis and the finding of Bence Jones protein in the urine. All patients had one or more of these significant abnormalities. Radiological evidence of myelomatosis has been present in many patients. The patients surveyed comprise all those seen in this department since 1958, the time at which melphalan became readily available.

### Methods

In this analysis patients fall into one of four groups of treatment:

#### 1. Patients receiving no specific anti-tumour treatment

Eleven cases in this series were given no specific treatment for myelomatosis because they came under care at a stage when they appeared moribund. In spite of this however two patients in this group continue to survive in good health a number of years after their presentation and they have needed no specific treatment since.

#### 2. Radiotherapy group

Nine patients come in this group and all presented early in the period under review. Radio-

therapy was usually given extensively to the spine or to local areas in which there was pain; radio-active phosphorus has been given intravenously to some patients to produce whole-body irradiation.

### 3. Other chemotherapeutic agents

These were given to six patients and the agents used were either urethane, cyclophosphamide or nitrogen mustard.

### 4. Patients treated with melphalan

This drug was given to thirty-six patients. In common with many other centres we were uncertain of the optimum dosage regime. Initially we employed an oral dose based on the patient's weight, of 0.075 mg/kg day for 10 days. At this time, however, the lag-response of the haemopoietic system and the wide range of individual sensitivity to the drug were not appreciated. Some cases produced profound toxic symptoms whilst others achieved little or no benefit from melphalan given in this dosage.

As has been noted by the Acute Leukaemia Co-operative Group B, we found that the most valuable parameter to use as a guide in the initial dosage was the platelet count, the dose being adjusted to bring the count down to 150,000 cells/mm<sup>3</sup>. The therapeutic ratio seems to be particularly narrow when the drug is first started, but subsequently melphalan can be given on a more empirical dose/weight programme. The point at which one changes to the latter is based on clinical findings, particularly the patient's subjective improvement; special tests and radiographs will not necessarily reflect this improvement until later in the course of treatment, if at all.

Maintenance therapy using melphalan is based on intermittent courses given at intervals of 12 weeks and lasting 1 week. Seventy milligrams are given orally (as is the initial course) in 1 week for a patient of average build (70 kg), that is 0.15 mg/kg day. Prior to 1963, our maintenance dose was 0.10 mg/kg/day, but since starting the higher dosage, we have been able to achieve a better survival (Fig. 2).

### Additional therapy

Complications such as hypercalcaemia, renal failure and anaemia have been treated concurrently with the causative disease whenever possible. Radiotherapy has been given to some patients but only to local areas such as when there has been a persistently painful bone deposit or a spinal lesion likely to cause cord compression. In a few patients steroids and androgens have been given in order to try to improve the level of

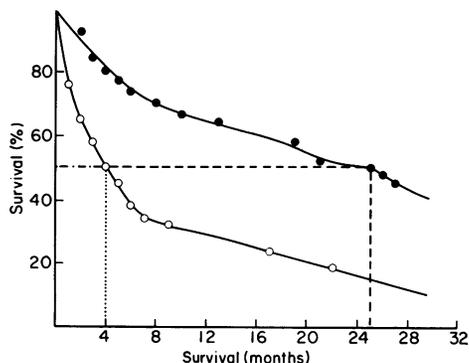


FIG. 1. Comparison of crude survival times of patients with myeloma. One group treated with melphalan (●), the other group not treated with melphalan (○).

circulating haemoglobin when there was severe anaemia.

### Results

#### 1. Mortality in the early months after diagnosis

The somewhat inelastic regime adopted when melphalan was first used led to over-dosage in some patients. This resulted in severe haemorrhagic episodes due to thrombocytopenia in seven patients which were fatal in five. In another seven patients neutropenia was severe enough to contribute to a fatal lung infection. However, since 1963 when the initial treatment was altered these complications have not been seen and there has been a distinct improvement in the percentage of patients surviving the first 6 months of treatment (Fig. 2).

However, in all four groups of patients under treatment rapid deterioration and early death occurred in a small percentage. When these

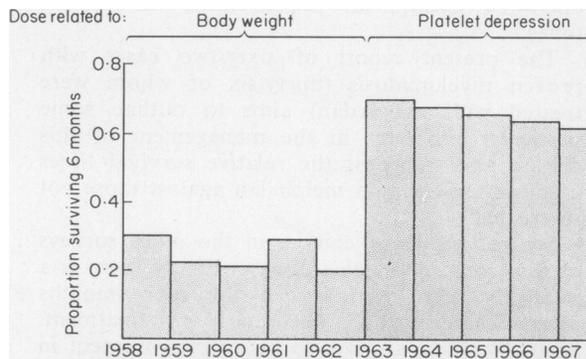


FIG. 2. Proportion of patients treated with melphalan surviving 6 months before and after change in therapeutic schedule.

patients were analysed in terms of the duration of their symptoms it was found that early death was most frequently correlated with a long history of symptoms regardless of the type of treatment given. Five factors appeared to be involved in the early death of patients seen with this disease. One factor was the rather intensive course of melphalan used in the early years of our experience with this drug, which resulted on several occasions in bone-marrow failure. However, marrow depression has not been seen in patients treated with the drugs during the established maintenance phase and it seems to us that in the early stages of the treatment of this disease patients may be more susceptible to its toxic effects on the bone marrow. A second factor was progressive uraemia. This could either be attributed to advancing disease or to the renal failure associated with massive tumour breakdown which is well known to occur during the use of radiotherapy or chemotherapy. The administration of alkalis or allopurinol during this period of treatment will usually prevent the uric acid nephropathy which is the cause of the renal failure. In those patients with renal failure only two showed the classical renal amyloidosis. A third factor contributing to early mortality was hypercalcaemia which presented as part of the initial symptom complex of the disease in seven patients. This complication often proved highly resistant to treatment and six of our patients died with persistent hypercalcaemia, although in four of these patients improvement was obtained from the administration of steroids. A fourth factor was severe anaemia which was benefitted only temporarily from transfusion of either whole blood or platelets. The patients showing severe anaemia usually had other symptoms of marrow failure such as neutropenia or thrombocytopenia, which contributed to their early deaths. The fifth factor was infection which was most often pulmonary. Septicaemia occasionally was the result of infection with unusual organisms such as *Pseudomonas pyocyanea*. Neutropenia was sometimes a factor contributing to infection but, in addition, abnormal antibody production was undoubtedly an important predisposing cause.

## 2. Median survival of patients treated with melphalan

Fig. 1 shows the median survival rate of patients treated with melphalan which is about 25 months. Compared with other patients in these groups this is a distinct improvement although too much weight cannot be put on the differences in these figures because an element of selection has undoubtedly been involved in the distribu-

tion of patients amongst our groups. However this median survival time compares very favourably with that found in other groups of patients not treated with melphalan in which it is less than about 8 months. It is clear, therefore, that melphalan improves the survival time of patients with myelomatosis. Apart from that increase in survival time, the quality of life of patients treated with melphalan was also remarkably improved. Relief of severe intractable skeletal pain was an almost invariable feature of patients treated with this drug. Patients who were bed-ridden with severe pain from extensive osteoporosis eventually become fully ambulant after such treatment. Undoubtedly local treatment with radiotherapy to pathological fractures or local areas of vertebral collapse contributed to the clinical improvement in some patients but such treatment was required in relatively few patients.

## 3. Resistance to melphalan treatment

Apart from those patients who died early during the course of treatment from the complications which have been mentioned all other patients responded satisfactorily to their first courses of melphalan. Most of them remained well for several years on this drug, but of those who have died, death could not obviously be attributed to resistance to treatment. However, two patients in this series have clearly become resistant to melphalan and have subsequently responded to treatment with cyclophosphamide.

## Discussion

In this series of patients with myelomatosis treatment with melphalan has improved their survival about three-fold over patients not treated or treated by radiotherapy alone. In addition to the improvement in survival we have been impressed by the symptomatic improvement experienced by our patients and which has been observed already in other centres.

Although melphalan should in our opinion be considered the mainstay of therapy for this disease, there are other important modes of treatment which should be available and should be used when there is any indication that the response to melphalan is slow or incomplete. These include radiotherapy, other chemotherapeutic agents such as cyclophosphamide and additional supportive treatment with blood transfusion and androgenic or adrenocortical steroids which may help to combat anaemia and neutropenia.

A comparative study of available chemotherapeutic agents should be interesting in terms of pure survival but we feel it is important not to introduce too rigid a format for the management

of individual cases as the addition of more than one form of treatment may be beneficial, particularly if resistance to one or other drug tends to occur. Having achieved a median survival-time of 25 months it should be possible to take treatment a stage further and produce a survival pattern closer to the normal non-malignant survival curve. Treatment in reverse-barrier wards to avert infection and the dialysis of patients showing renal failure together with the use of donor-marrow transfusion may all be methods of treatment worth exploring to enhance the present rates of survival.

Although melphalan is a potent and useful drug it appears to have a rather narrow therapeutic margin of use and without particular care death in the early stages of disease may be partly brought about by this treatment. Other agents such as cyclophosphamide undoubtedly have a safer therapeutic margin. Where dosage control based on frequent blood counts cannot be carried out results as favourable may be expected. After the initial period of close haematological supervision it has only been our practice

to review patients at monthly intervals. This has been possible because of the intermittent administration of the drug; other centres which have given continuous chemotherapy have required patients to attend twice a week for blood counts which results in an additional burden on patients and technical staff. Although we would like to increase the interval between hospital attendances if possible, the occurrence of unexpected neutropenia or new symptoms occurring between visits has prevented us extending the monthly intervals of attendance.

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