Today's Treatment

Blood and Neoplastic Diseases

Myelomatosis

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The successful management of myeloma requires not only the use of radiotherapy and chemotherapy but also treatment of the anaemia, infections, bone fractures, metabolic disturbances such as hyperuricaemia and hypercalcaemia, and renal failure that may complicate the course of the disease. Recent advances in the study of myeloma cells and their growth rate and behaviour have resulted in new concepts about the development of this tumour and have a bearing on management.

Diagnosis

The diagnosis of myeloma is usually based on the demonstration on serum electrophoresis of a homogeneous band of paraprotein or "M" component, on the detection of Bence Jones protein, the light chain moiety of immunoglobulin in the urine, and the finding of bone marrow plasmacytosis with destruction of the bone on radiography. At the time it presents clinically myeloma is a relatively slowly growing tumour, though this may not be true in the early part of its development.¹ During the clinical course of the disease myeloma cells divide about once every six months, and when symptoms and signs are present there is already a large burden of tumour in the body of about $0.5-1.2 \times 10^{12}$ cells.

The size of the tumour burden can be estimated from the rate of production of paraprotein produced by all the myeloma cells and by determining the production rate of paraprotein from one cell. The greater the tumour mass the more likely are complications such as bone destruction, hypercalcaemia, anaemia, and renal failure. Though determination of the number of myeloma cells present is possible for each patient, the procedure is difficult. Salmon and his colleagues² have shown that 16 readily available clinical features (for example, haemoglobin, bone lesions, serum calcium, albumin, M-protein, weight loss, fever, performance status) correlated well with the measured tumour cell numbers in 54 patients. This simple accurate system is used as a staging system in a multiinstitutional study by the Southwest Cancer Chemotherapy Group. With the use of a computer it is also possible to make serial determinations of the tumour mass and assess the response to treatment.

Treatment with the most effective chemotherapeutic agents available reduces tumour mass by only about 1-2 logs since evidence of myeloma protein production is still detectable in most responding patients. Even so, because it is such a slowly progressive tumour, this will increase the median duration of survival from the nine months in untreated patients to the 20 months or more in treated

and responsive patients. Animal studies have suggested that, as it is reduced in size by treatment, the behaviour of the tumour may alter, and as reduction in size occurs the percentage of proliferating myeloma cells increases.

Apart from this change in behaviour, it might be asked if there are any other reasons why such a slowly growing tumour should be so difficult to control effectively. Chemotherapy with alkylating agents such as melphalan or cyclophosphamide may become ineffective owing to the development of resistance. Resistance to one alkylating agent has deterred the use of another, but experimental evidence in animals and a clinical study³ suggest that cross-resistance of alkylating agents may not occur in all patients with myeloma and it is justifiable to try another alkylating agent. If a second alkylating agent can be used then this may well help to extend the period of control, but bone marrow suppression and other toxic side effects may, of course, prevent further administration. The tumour itself may show changes in growth kinetics, certainly after successive relapses.⁴ This laboratory finding is reflected in a recent study by Bergsagel,⁵ who reported the clinical course of 50 patients with myeloma who have had a succession of relapses. In 17 patients the illness terminated with an acute phase characterized by fever, pancytopenia, a hypercellular bone marrow, a fall in the paraprotein, and a total lack of response to conventional treatment. Bergsagel has drawn an analogy with the "blast" crisis of chronic myeloid leukaemia and suggests that the exploration of new forms of chemotherapy to deal with this "crisis" phase of myeloma are justified. Improvement in survival may come from a better use of the agents already available, and possibly the recognition of a time in the clinical course when chemotherapeutic drugs other than alkylating agents may help.

Response to Treatment

To make these advances improvement in the objective measurement of response is necessary. Alexanian *et al.*⁶ have defined quantitatively the improvements in clinical and pathological findings that correlate with improved survival. Relief of pain, increase in performance, a rise in the level of haemoglobin, a rise in the serum albumin level and a fall in the blood urea level, together with recalcification of the skeletal lesions are all related to improved survival—but the most reliable criterion was a definite fall in the rate of "M" component production calculated from the serum concentration or the Bence Jones protein excretion. Reduction of up to a half had little effect on the outlook, reduction of 50% to 75% had a significant influence, but a reduction to 90% (which must represent a considerable destruction of tumour) had a definitely satisfactory influence on survival. A similar reduction in the excretion of Bence Jones protein was also equally beneficial. These stringent criteria

enable the comparative evaluation of drug regimens to be carried out with greater confidence, but they make comparison with earlier studies of treatment more difficult unless the data are evaluated in an identical manner.

Chemotherapy

The alkylating agents melphalan and cyclophosphamide are firmly established as effective in myeloma and will be discussed in detail. After many years the effectiveness of prednisolone as specific treatment has been questioned by Bergsagel because of the possibility that the "M" component is reduced specifically by increasing its rate of removal. In controlled trials Cuttner⁷ showed that melphalan and prednisolone were more effective than melphalan alone. This was because prednisolone helped to reduce mortality in poor risk patients early in the course of their disease; survival was not prolonged. This effect of prednisolone could have been due not to antitumour action but to non-specific benefit by raising the haemoglobin concentration or controlling hypercalcaemia, for example. Nevertheless, most investigators in the U.S.A. have concluded that prednisolone combined with alkylating agents contributes significantly to a higher response rate.

Several new drugs have been investigated for their effectiveness in myeloma by the Southwest Oncology Group. Alexanian *et al.*⁸ evaluated the activity of procarbazine and vincristine in producing and maintaining remission. Previously untreated patients were randomized to treatment with melphalan and prednisolone alone; melphalan, prednisolone, and procarbazine; or melphalan, prednisolone, procarbazine, and vincristine. In a study of 508 patients remission rates were 47%, 46%, and 50% for the three groups; the differences were not significant. Thus these investigators concluded that neither procarbazine nor vincristine had any useful role in the treatment of patients with myeloma.

In the first study ever undertaken of continuation or maintenance treatment in myeloma, the patients who went into remission were randomized to treatment with melphalan and prednisolone; bischloroethylnitrosourea and prednisolone; or no specific treatment. No differences were seen in the remission duration or survival times in the three groups. It was concluded therefore that maintenance treatment with either of the two regimens offered no advantage to responsive patients after the first year—and indeed the incidence of intercurrent infection was higher in the treated group.

ALKYLATING AGENTS

Earlier studies using melphalan or cyclophosphamide in continuous doses showed a significant increase in the survival of treated patients compared with results from a retrospective analysis of myeloma patients treated without their use. Moreover, those that responded to either agent survived longer than those who did not respond. In an M.R.C. co-operative trial in myeloma⁹ melphalan and cyclophosphamide were shown to be equally effective in producing a response. The results of several studies in which there has been variation in dosage and timing of both of these drugs are now available and I will review them briefly.

Melphalan (Phenylalanine Mustard)

For some years I have used a modification of the schedule recommended by Alexanian⁸ giving melphalan 0.15 mg/kg/day for four days together with prednisolone 40 mg daily for the same period, with intervals of six weeks between courses.

If the regimen is tolerated and no serious marrow suppression occurs, the length of the courses is gradually extended to seven

days. Intermittent treatment allows recovery of normal tissues and it also has advantages in treating ambulatory patients because blood counts are required only every four to six weeks. Cyclophosphamide is more toxic for proliferating cells than resting cells and this was thought to be true also for melphalan. It has recently been shown that this is not so and the rationale for the intermittent use of melphalan may not be correct. In theory it should be used in continuous low dosage.

The only controlled trial¹⁰ which has tested continuous versus intermittent treatment may have used too small a dose in the continuous melphalan arm of the trial, the rather poor response rate of 19% possibly resulting from inadequate treatment rather than the method of giving the drug. Nevertheless, several different regimens using both intermittent and continuous administration have shown similar results in terms of response and survival, and probably this indicates that the aspects of cell kinetics studied so far have a relatively trivial role in determining the effect of treatment. At the moment the intermittent regimens outlined at the beginning of this section are effective, well tolerated, and easy to handle in the clinic.

Cyclophosphamide (Endoxan)

Cyclophosphamide has been used most often in continuous dosage. The usual dosage has been 2 mg/kg/day and this has been varied according to the peripheral blood count.

Animal studies have suggested that intermittent cyclophosphamide may be more effective. Bergsagel³ treated myeloma that was no longer responsive to melphalan with intermittent cyclophosphamide with satisfactory results. Cyclophosphamide was given either intravenously in a dose of 1 g/m² or orally 0.25 g/m²/day for four days. The single intravenous injection or course of oral drug was repeated at intervals of three weeks. The oral intake of fluid was increased during treatment. Nineteen patients were treated, with a good response in six and a partial response in five. There are, so far as I know, no results of comparative trials of intermittent versus continuous cyclophosphamide.

Cyclophosphamide may be less toxic to the bone marrow than melphalan at equivalent dosage, and it particularly spares platelet formation. It may be helpful in patients with a poor marrow reserve and in elderly patients in particular. Alopecia may be a problem, but fortunately the provision of an acceptable wig is not difficult. Haemorrhagic cystitis which is due to toxic metabolites of cyclophosphamide may to some extent be prevented by increasing fluid intake. If it occurs the drug should be stopped. It is not wise to administer continuous cyclophosphamide for over a year.

Intermittent melphalan and prednisolone seem to be the most effective agents for inducing remission in myeloma. If remission is not achieved or there is early relapse intermittent cyclophosphamide may be successful. There is increasing evidence that continuous maintenance for over a year with melphalan and prednisolone, or combinations including cyclophosphamide or B.C.N.U. are not only ineffective but have a deleterious effect on the patient's health. There is an urgent need to find more suitable maintenance agents in myeloma.

Bone lesions

Bone pain and the resulting immobility are among the most distressing symptoms of myeloma. Radiotherapy is used to treat a local painful lesion. Relief is prompt and, if it is not, then the possibility of an unrecognized pathological fracture in a long bone, for example, should be considered. Extensive radiotherapy is contraindicated for patients with generalized disease, as an adequate bone marrow reserve may be compromised. Chemotherapy may relieve pain but many large studies have shown that recalcification of the skeleton is unusual with chemotherapy alone. In a group of patients with lytic lesions of the skull, half responded to melphalan therapy but of these only 30% showed recalcification.¹¹

Sodium fluoride has been administered to strengthen the bones of patients with myeloma, on the grounds that the dense fluorosis that occurs might do this and prevent spontaneous fractures. In a trial of low and high dose fluoride administration compared with a placebo Harley *et al.*¹² were unable to show any differences between the three groups in survival, progression of skeletal change, loss of height, incidence of pain, loss of performance, or requirement for radiotherapy. They concluded that by itself fluoride made no difference. Carbone *et al.*¹³ studied the bone formed after giving fluoride and found that it contains no more calcium as a result, the bone being inferior in quality and just as likely to fracture. Others have felt that the concurrent administration of vitamin D, calcium, androgen, and fluorides may be effective, but there are no controlled studies on this point. It seems that fluoride by itself is of little benefit.

Hypercalcaemia

A major metabolic complication involving bone is hypercalcaemia. A complaint of general weakness, tiredness, lassitude, anorexia, nausea, vomiting, thirst, constipation, drowsiness, or even abnormal mental behaviour should raise the possibility of this complication and the diagnosis is confirmed by showing a raised serum calcium level. Mild symptoms with a slight rise of the serum calcium level may be managed by a low calcium diet, increased fluid intake, and immediate and effective chemotherapy. If this fails then prednisolone in a daily dose of 60 mg with oral neutral phosphate in doses of 1 to 2 g in the first 24 hours is effective. Until chemotherapy controls the tumour disodium hydrogen phosphate, 10 g daily (a total daily phosphate administration of 2 g), will be needed to keep the serum calcium level within normal limits.¹⁴ Theoretical objections that calcium may be deposited in vital areas such as the kidneys must be considered in relation to the situation of a patient with steroid-resistant hypercalcaemia, a life-threatening occurrence. The role of calcitonin, glucagon, and diphosphonates is under investigation.

Viscosity Syndrome

Plasmapheresis is the method of choice for treating the viscosity

syndrome in macroglobulinaemia or myeloma. This syndrome—which may give rise to a variety of symptoms such as deterioration of vision with eventual blindness, a reduced level of consciousness ending in coma, heart failure, renal failure, and intractable bleeding—is caused by increased plasma viscosity due either to excess of the “M” component or to large polymers formed from it. In patients who bleed probably several factors (including coating of the platelets, inhibition of thrombin activity, or adsorption of clotting factors) are responsible for the damage to the mechanism of coagulation. The N.C.I.-I.B.M. Cell Separator which is designed for the collection of leucocytes from the peripheral blood may be used as an efficient and safe method of plasma exchange.¹⁵ There is a dramatic arrest of bleeding or recovery of consciousness after its use.

Progress in the management of myeloma has been disappointingly slow. Nevertheless, the demonstration that cross resistance to alkylating agents may not be present, our continuation or maintenance treatment is inadequate, and the understanding of the kinetics of the myeloma cell, should stimulate new approaches to the management of this disease.

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Imported Diseases in General Practice

Gastrointestinal Disorders

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Gastrointestinal upsets must be as common throughout the world as upper respiratory infections. In 70-80% of cases the cause is unknown, the illness is shortlived, and the patient does not seek medical advice. Precisely because the upset is usually trivial, ready access to doctors in Britain means that the traveller runs

the twin risks of over-treatment and failure to diagnose serious conditions. As usual, a careful history with particular attention to the patient's social and geographical background, together with some knowledge of the distribution of disease for which Professor Brian Macgraith's small book is invaluable,¹ are more likely to influence the outcome than indiscriminate use of drugs such as antibiotics, whose value is doubtful.

No one is immune from gastrointestinal upsets, but the young—for example, schoolchildren returning from holidays abroad—and the elderly are particularly susceptible and often suffer more serious disease. Moreover, the immigrant population of Europe is more mobile than it used to be and it is important to ask a

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