Difficult Decisions

Problems in the management of myeloma

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While there can be no doubt that the middle-aged patient who presents with the classical form of myeloma uncomplicated by renal failure needs prompt and effective specific chemotherapy, there are undoubtedly some patients with paraproteinaemia that give rise to difficulty. The problem of benign monoclonal gammopathy, or, as it is more appropriately called 'monoclonal gammopathy of undetermined significance' (MGUS)¹, is now a well-recognized entity. The presence of little clinical disability, a low level of paraprotein, the absence of lytic lesions in the bones and of Bence Jones protein in the urine, clearly indicate a 'benign' course and no treatment is required. However, some patients with a small quantity of paraprotein do have up to three small lesions in the bone, and may also be anaemic with haemoglobin of under 10 g/dl. These patients, with indolent myeloma² or smouldering myeloma,³ appear to have stabilized with a low level of paraprotein. Although they generally show progress to overt myeloma in 3 to 5 years, it is considered unwise to start active specific therapy before that time. Their progress can be monitored by regular estimation of paraprotein and bone radiology.

Two clinical complications that may present special problems, either at presentation or subsequently during the course of the disease, are hypercalcaemia and renal failure. Approximately 30% of cases are hypercalcaemic at presentation.^{4,5} It is now recognized that bone damage and liberation of calcium into the extracellular fluid is not confined to the lytic lesions in the bone, but is a generalized process in which the activity of osteoclasts and osteoblasts is no longer controlled in a complementary fashion, but becomes uncoupled.⁶ Thus the removal of bone by the osteoclasts is not followed, as in the normal condition, by attraction of osteoblasts with laying down of bone and remodelling. Specific factors are now known to act on the 'uncoupled osteoclast', resulting in its increased activity. Tumour necrosis factor β and interleukin-1 form part of a complex group of cytokines which are components of an osteoclast-activating factor (OAF).

Knowledge of these factors has allowed a more rational approach to therapy. Agents are now available which can prevent the activity of these cytokines.^{7,8}

A frequent problem in the management of the elderly patient with hypercalcaemia is that they may often have concurrent heart disease. One of the most important methods of reducing serum calcium is by giving large volumes (3–6 litres) of normal saline, but this may readily precipitate heart failure in these patients from fluid overload, particularly if they are also given the customary 30–100 mg of prednisolone.⁹ The fall in calcium may be delayed for hours or even weeks, during which time the patient may go into intractable heart failure despite loop diuretics such as frusemide. Calcitonin may help, but its effect is usually transient: mithromycin is effective, but produces thrombocytopenia, delaying specific therapy, and oral phosphate may work but produces unpleasant gastrointestinal disturbance with diarrhoea.

Faced with this dilemma, the use of bisphosphonates, etidronate or clodronate, may be helpful. Etidronate¹⁰ should be given as an infusion over 3 hours to avoid renal damage. This effectively relieves bone pain and will reduce serum calcium when given daily for 3 days. Its prolonged use may inhibit recalcification of bone, but as reconstruction of the bony skeleton does usually start once specific chemotherapy has been instituted, this difficulty may be more theoretical than real. It does appear that clodronate, by contrast, actively encourages the deposition of calcium in bones, but further evidence for this is needed.¹¹

Renal failure is often associated with hypercalcaemia, but may be an independent complication. The blood urea and creatinine is raised in more than 50% of patients presenting with myeloma,⁹ and this has a bad effect on prognosis. A problem may be faced with determining how aggressive management should be in elderly patients who present with the features of renal failure. Some of them may be dehydrated, and treatment of hypovolaemia, associated hypercalcaemia and infection may result in restoration of renal function to normal. Thus specific intervention may be justified after a few days when the urea and creatinine levels have returned to normal. In the younger patient,

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particularly those with light chain excretion, irreversible changes in renal function may have occurred. Even in these patients, specific therapy may hold the promise of several years of useful life, and in the younger patient, establishment of regular dialysis is justifiable.

Specific therapy is beginning to present a problem in that there are now an increasing number of options. Conventional treatment with melphalan and prednisolone can be shown to produce a response in about half the patients treated. Median survival of these patients is some 30 months. Cyclophosphamide is also effective as a single agent. Alternative four- or five-drug combinations with an anthracycline, nitrosourea, and vincristine are also well-established and have undergone extensive clinical trials, particularly in the United States.¹² More recently, infusions of vincristine, doxorubicin and high-dose steroids such as dexamethasone in the VAD regimen¹³ and methyl prednisolone in the VAMP regimen¹⁴ have been shown to produce a good rate of response, but these are unfortunately of relatively short duration. Programmes in which high-dose melphalan, with or without the use of autologous bone marrow transplantation to support the patient through the haematological nadir, have also been published, and appear to improve survival in selected patients.^{15,16}

Alpha interferon has been shown to have an effect on the myeloma cell. Currently the effect on overt disease is disappointing, but recently Mandelli and his colleagues¹⁷ have shown that it may improve the duration of remission. Randomized trials are now under way to confirm this assertion, and if this is true, it will do much to alleviate the problem of relapse, which has been such a feature of chemotherapy programmes so far.

When faced with the problem of what to do, it has to be admitted that at the present time no treatment is

curative. High-dose melphalan is still an experimental procedure which has been reserved for fit patients under the age of 65, and should be carried out in special centres.

There is no evidence that the multidrug regimens give any benefit to myeloma patients over the age of 65, and in elderly patients with poor performance status, these regimens have actually been shown to shorten life. In the younger patient there is an enhanced response rate, and a modest, though useful, improvement in the duration of survival is reported in some series, although Bergsagel¹² in a 'meta-analysis' could find no real evidence of an improvement in long-term survival.

Melphalan and prednisolone remains the treatment of choice in the frail patient with myeloma over the age of 65. If the condition is complicated by renal failure which persists after treatment of such factors as dehydration and hypercalcaemia, then cyclophosphamide can be safely substituted for melphalan. In the younger, fitter patient it is justifiable to enter them into the national studies of specific therapy, or to refer for high-dose therapies associated with bone marrow transplantation at one of the appropriate special centres.

Conclusion

Improved understanding of the mechanisms of calcium loss from the bones in patients with myeloma will lead to a decrease in the morbidity and mortality in these patients. Development of safer methods of inducing a complete response with actual elimination of all detectable myeloma cells and of the 'M' band will undoubtedly improve results and lead to an increase in survival.

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