Leading Article

New treatments in myeloma - is cure possible?

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Myeloma is a malignancy of the plasma cells derived from the B lymphocyte series. It is characterized by early and wide dissemination of tumour cells resulting in bone destruction, anaemia, infections, hypercalcaemia, renal failure and occasionally symptoms of hyperviscosity. The myeloma cells may either produce local destruction of bone or produce paraprotein ('M' band in the serum), or the light chain moiety of the paraprotein which is excreted in the urine as Bence Jones protein. The quantity of the 'M' band correlates closely with the tumour mass, stage of disease and parallels the response to therapy.¹ The median survival time (MST) of patients with myeloma who have not received specific therapy is 17 months.

Comprehensive reviews of specific therapy have examined progress over the last decade.^{2,3,4} Specific chemotherapy began with the introduction of urethane, cyclophosphamide and melphalan in the late fifties. Urethane was ineffective in prolonging survival, but cyclophosphamide and melphalan not only produced clinical responses but resulted in increased survival.^{5,6} After many hundreds of patients with myeloma have been treated with melphalan and prednisolone in various trials, it is evident that about 40% achieve a response and that the MST is some 30 months.³ This combination is the one to which all others are currently being compared. Although subjective and objective responses may be seen, melphalan and prednisolone are not curative.

In order to improve these results additional drugs have been added to melphalan and prednisolone. Since other alkylating agents might not show cross-resistance, Lee *et al.*⁷ combined vincristine, BCNU, cyclophosphamide, melphalan and prednisone in the M2 programme at the Memorial Sloan Kettering. This gave a response rate of 48% and an MST of 38 months. The combination was compared with historical controls so that the improvement may not only be due to the combination. Nevertheless, long term survival was not seen.

The development of the technique of randomized trials has allowed a very large number of studies comparing combinations of multiple drugs with melphalan and prednisolone. In summary, the addition of other alkylating agents and the nitrosoureas has not proved beneficial in terms of a significant increase in response or survival. A trend towards improvement when the anthracycline doxorubicin, alone or in combination with vincristine, has been used, is apparent in a number of these studies. For example, in the South-west Oncology Group study⁸ a significant benefit occurred in patients with Stage III disease who received vincristine and doxorubicin in their multidrug induction therapy.

This gave encouragement to the use of non-alkylating agent-containing regimens such as vincristine, adriamycin (doxorubicin), and high-dose dexamethasone (VAD) introduced by Barlogie *et al.*⁹ Fourteen out of 29 patients (70%) showed a reduction of 75 % in their tumour mass. Remissions occurred even in patients who were known to be resistant to alkylating agents. In an update on the use of VAD in resistant multiple myeloma, 63% are noted to have responded¹⁰ with an MST of 21 months in the 28 responders.

A somewhat different approach has been the use of effective drugs as single agents, but in very much increased dosage. Two groups of drugs, steroids and alkylating agents, have been explored. The use of high-dose dexamethasone as part of VAD was validated in the study by Alexanian *et al.*¹⁰ when 25% of the patients previously resistant to melphalan responded to high-dose dexamethasone alone. Pilot studies using large doses of methyl prednisolone have also proved the effectiveness of this approach, when used in a dose of 1 g/day for 5 days. Nevertheless, as would be expected, these responses are not durable.

McElwain & Powles¹¹ showed that the magnitude of the response of myeloma to melphalan is dose-dependent. An extended study¹² has shown that melphalan in a dose of 140 mg/m² in previously untreated patients with Stage III disease can produce remissions in which no myeloma cells are seen in the marrow, no paraprotein is present in the serum, and levels of immunoglobulins return to normal. Forty one

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previously untreated patients under the age of 63 have been given high-dose melphalan. Eleven have achieved complete disappearance of all manifestations of disease described, and all are alive with a maximum follow-up of 50 months and a median of 20 months.

Even so, some patients in this group have shown return of their disease, and it is planned to escalate the dose still further in order to prevent these relapses. The role of autologous bone marrow support is being explored, although currently no method of purging malignant cells in the bone marrow is available. The

outcome of these studies (which are at an early stage) will be of not only clinical but theoretical interest, for there is a possibility that the myeloma cells remaining in the marrow after initial effective therapy may not be clonogenic.

It has been disappointing that the intense effort devoted to multidrug combinations has been so unrewarding, and that biological response modifiers such as interferon have failed to live up to their promise. The next few years should see an answer to the question whether high-dose drug therapy has anything to offer patients with myeloma.

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