

Newer Approaches to the Therapy of Multiple Myeloma

PROGRESS IN the management of multiple myeloma has been modest since the introduction of melphalan more than a quarter century ago. Oral administration of melphalan (L-phenylalanine mustard; Alkeran) and prednisone is a standard form of therapy but produces objective response in only 50% to 60% of patients. The dosage of melphalan should be modified so that some reduction in leukocytes and platelets occurs 3 to 4 weeks after the beginning of each cycle because of the variability of absorption. Melphalan and prednisone should be given for 1 to 2 years and then discontinued if the M-protein levels in the serum and urine have been stable for at least 6 months (plateau state) and if the patient has no other evidence of active disease. Chemotherapy should not be discontinued during the first year unless there is definite evidence of progression of disease, because some patients with a low plasma cell proliferative index will not obtain an objective response until the second year. The obvious shortcomings of melphalan and prednisone have stimulated investigators to use many combinations of chemotherapeutic agents. A major controversy in chemotherapy of multiple myeloma is whether melphalan and prednisone are as effective as a combination of alkylating agents. Ten prospective randomized trials of melphalan and prednisone versus a drug combination failed to clearly show that drug combinations were better than melphalan-prednisone in the treatment of multiple myeloma.¹ The unfortunate truth is that neither single nor multiple drugs are adequate. New agents or modalities must be found before treatment of multiple myeloma can be significantly improved.

α -Interferon (α -IFN), a biologic response modifier, may be a useful agent in initial therapy when used in conjunction with alkylating agents and in delaying relapse after induction chemotherapy. In a pilot study, 54 evaluable patients with previously untreated multiple myeloma were administered alternating 3-week cycles of VBMCP (vincristine, BCNU, melphalan, cyclophosphamide, and prednisone) and r-IFN α_2 . Objective responses occurred in 80% of the patients, with 30% having a complete response (CR) and 16% having a near-complete response (NCR). Thirteen of the 25 patients with CR or NCR are still in first remission. The median survival was 40 months.² These encouraging results must be confirmed in a prospective study. Mandelli et al³ reported that r-IFN α_2 b prolonged response duration and survival in patients with multiple myeloma who had responded to conventional induction chemotherapy. Relapse occurred in 25 of the 50 patients (50%) in the r-IFN α_2 b maintenance group and in 41 of the 51 patients (80%) in the control group. Twenty-one (42%) of the 50 patients in the IFN group and 8 (16%) of the 51 patients in the control group are alive and remain free from progression. The median duration of response was 26 months in the IFN group and 14 months in the control group ($P = .0002$). The overall median survival was 52 months in the IFN group and 39 months in the control group ($P = .05$). However, no significant difference in survival was observed among patients who had only disease

stabilization at the end of induction chemotherapy. This is an encouraging study, but it requires confirmation.

Bone marrow transplantation is an alternative modality for therapy of multiple myeloma. In a series of five patients with identical twin bone marrow transplants (syngeneic), three had relapse of their myeloma at 6, 17, and 18 months; one died at 1 month from cytomegalovirus-associated interstitial pneumonitis; and the fifth was alive and well after 5.5 years but had a small, persistent monoclonal serum protein.⁴ Ten of 14 patients with multiple myeloma who received an allogeneic bone marrow graft from an HLA-compatible sibling donor survived for a median of 12 months. Five of the 10 patients had no signs of active myeloma, four had minimal persistent disease, and one was in relapse.⁵ There is a significant immediate mortality, the risk of graft-versus-host disease is high, and most patients with multiple myeloma are ineligible for allogeneic transplantation because of their age. Thus, allogeneic bone marrow transplantation is of limited use in the management of multiple myeloma.

Autologous bone marrow transplantation is potentially applicable for more patients because the age limit is higher and a matched donor is unnecessary. However, two major problems exist. First, the complete eradication of multiple myeloma from the patient may not occur, even with large doses of chemotherapy and radiation. The second major problem is that of reinfusing autologous marrow contaminated by myeloma cells or their precursors. This is a potential source of relapsing disease. Purging of the marrow in vitro with a combination of monoclonal antibodies and/or cytotoxic agents is being investigated, but is not yet suitable for routine clinical use. Furthermore, it has not been proven that removal of mature plasma cells is beneficial or necessary. The use of peripheral blood stem cells for marrow reconstitution after high-dose chemotherapy and radiation is attractive because there are potentially fewer myeloma cells in peripheral blood than in the bone marrow. Stem cells from autologous peripheral blood have successfully reconstituted the marrow of multiple myeloma patients treated with high-dose chemotherapy and total body irradiation.⁶

The Royal Marsden Group gave 50 previously untreated patients with multiple myeloma repeated cycles of vincristine, Adriamycin (doxorubicin), and methylprednisolone (VAMP). Treatment with VAMP was continued until the M-protein was stable or undetectable. High-dose melphalan was subsequently administered followed by autologous bone marrow rescue. Twenty-five patients (50%) achieved a complete hematologic and biochemical remission. The high CR rate is impressive, but 5 of the 25 patients in CR have already relapsed.⁷

In this issue of *BLOOD*, Jagannath, et al⁸ reported 55 patients with multiple myeloma treated with high-dose melphalan or thiotepa and total body irradiation before an unpurged autologous bone marrow transplant. Fourteen patients in relapse were resistant to chemotherapy and fared poorly: 5 of the 14 had an early death, none obtained a complete remission and the overall survival was 7 months.

Among 41 remaining patients, there was only one early death and 27% achieved complete remission. Their projected 4-year survival rate was 82%. Seven of the 41 patients had not responded to initial chemotherapy, but unexpectedly 29% of them achieved a CR and a median survival of over 4 years. Fourteen of the 41 patients were previously untreated and obtained a remission after 4 to 6 cycles of VAD and had a survival greater than 33 months. It must be recognized that these 14 patients may have done well with conventional chemotherapy without the risk and expense of autologous bone marrow transplantation.

The capacity of granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF to shorten the duration of granulocytopenia has been explored in patients receiving high-dose chemotherapy. The administration of these growth factors produces increased granulocyte levels and a potential reduction in bacterial infections. Barlogie et al⁹ demonstrated that GM-CSF administered to patients with refrac-

tory multiple myeloma who were less than 50 years old and who had received chemotherapy for less than 1 year had significantly reduced periods of granulocytopenia (21 v 35 days) when compared with patients who had not received GM-CSF. The CSFs may play a significant role in reducing infection in aggressively treated patients.

Interleukin-6 (IL-6) is a potent growth factor for plasma cells and is elevated in overt myeloma and plasma cell leukemia.¹⁰ Preliminary studies using anti-IL-6 antibodies show activity in patients with plasma cell leukemia (Bataille, personal communication, June 1990).

There is a great deal of interest in multiple myeloma, and we all hope that generation of new data on the biology of the plasma cell will lead to improved therapeutic approaches.

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