Limited Value of Myeloablative Therapy for Late Multiple Myeloma

By Raymond Alexanian, Meletios Dimopoulos, Terry Smith, Kay Delasalle, Bart Barlogie, and Richard Champlin

The utility of myeloablative therapy supported by autologous bone marrow (BM) or blood stem cells was assessed in 49 patients with multiple myeloma who had received at least 1 year of prior chemotherapy. Outcomes were compared with those of similar patients who did not receive intensive treatment primarily for socioeconomic reasons. Among patients with disease in resistant relapse despite treatment with vincristine-doxorubicin by continuous infusion with pulse dexamethasone (VAD), a 61% response rate was associated with a median remission time of 5 months. After primary resistance for more than 1 year, 6 of 15 patients responded and the overall survival was similar to that of control patients. For patients with melphalan-resistant disease that responded to VAD, the remission time was similar to that of control patients. Current myeloablative treatments supported by autologous BM or blood stem cells were useful to very few patients with multiple myeloma after the first year of chemotherapy.

© 1994 by The American Society of Hematology.

For approval for these studies was obtained from the Institutional Review Board, and written informed consent was provided according to the Helsinki Declaration.

Treatment. Treatment for 26 patients consisted of a combination of melphalan (40 mg/m²) and total body irradiation (45 Gy; TBI) as described previously; thiopeta (750 mg/m²) was substituted in five patients when intravenous melphalan was unavailable for 9 months; since 1991, a combination of thiopeta (750 mg/m²), busulfan (10 mg/kg), and cyclophosphamide (120 mg/kg) was administered to 18 patients. Either autologous BM or blood stem cells collected by leukapheresis were infused intravenously within 48 hours after completion of TBI or high-dose chemotherapy. BM consisted of at least 2 × 10⁶ nucleated cells/kg and 1 × 10⁶ granulocyte-macrophage colony-forming unit/kg; blood stem cells were given to five recent patients with greater than 20% marrow plasmacytosis or an inadequate marrow harvest and consisted of at least 2.5 × 10⁶ nucleated cells/kg and 3 × 10⁶ CD34⁺ mononuclear cells/kg. All patients received prophylactic antibiotics, initially trimethoprim, sulafmethoxazole, and ketoconazole in a protected-environment room; since 1989, they received vancomycin, norfloxacin, fluconazole, and acyclovir in a private room. Previous reports have considered the times to granulocyte and platelet recovery, the toxicity, and the causes of treatment-related death. Most responding patients were maintained on interferon-α (1 to 2 million units/m², three times weekly) with dexamethasone (20 mg/m² each morning, for 4 days each month).

Staging and response. Plasma cell tumor mass was defined in each patient as high, intermediate, or low by standard criteria. Thus, high tumor mass required either Hgb less than 8.5 g/dL or serum calcium greater than 11.5 mg/dL; intermediate tumor mass was defined by Hgb between 8.5 and 10.5 g/dL or serum myeloma protein greater than 4.5 g/dL with normal serum calcium; low tumor mass required both Hgb greater than 10.5 g/dL and serum myeloma protein less than 4.5 g/dL. Clinical response was defined as a 75% reduction of serum myeloma protein production, disappearance of Bence Jones protein, and reduction of marrow plasmacytosis to less than 5%. Complete remission required the disappearance of serum monoclonal globulin on immunofixation studies. Seven patients (14%) died of treatment-related complications and were considered unresponsive.

Control patients. For each of the three disease phases under study, control patients were identified who also received VAD and met the eligibility criteria for myeloablative therapy, but did not receive such treatment. Most patients were contemporary with the transplanted patients and either refused intensive treatment, were denied coverage of the procedure by their insurance company, or were ineligible for TBI because of prior radiotherapy to the spine. The current overall remission rate was 39% received VAD without subsequent transplant during the 3 years before activation of the transplant protocol. As in patients who received intensive therapy, control patients were 62 years old or less, had Zubrod performance status of 0 or 1, were free of serious cardiac, pulmonary or renal dysfunction.
intensive therapy, in comparison with one of nine control patients (Fig 1). Remission after VAD was similar for comparable patients who had less marked reductions. Low levels of normal IgM (<50 mg/dL) doubled to the normal range in three of six patients. Although four patients responded for more than 15 months (range, 1 to 5 months), and there was one treatment-related death. Complete remission was confirmed in eight patients. Intensive therapy was given a median of 3 months after the onset of remission (range, 1 to 5 months), and there was one treatment-related death. Complete remission was confirmed in 4 of 10 patients with evaluable data in comparison with 1 of 14 control patients (P = .05); two additional transplanted patients showed greater than 75% decrease of residual tumor mass and four patients had less marked reductions. Low levels of normal IgM (<50 mg/dL) doubled to the normal range in three of six patients with evaluable data who received intensive therapy, in comparison with one of nine control patients (P = .10).

RESULTS

Resistant relapse. Intensive therapy induced responses in 61% of 23 patients with disease relapsing despite VAD. Treatment-related deaths occurred in four patients (17%), none achieved a complete remission, and the median survival was 8 months. When all patients are considered, the median remission was 3 months (5 months for responding patients) and no patient responded for more than 15 months (Fig 1). In all responding patients, the remission time after transplant was shorter than the first remission. Despite the slightly less advanced disease among transplanted patients (Table 1) (P = .18), survival after prior VAD was similar to that of 33 control patients (Fig 1). Response rates and remission times were the same regardless of the degree of plasmacytosis in transplanted marrow (range, 0% to 25%).

Primary resistance greater than 1 year. Among 15 patients with primary resistant disease for at least 1 year, there were two treatment-related deaths, six patients responded, and none achieved a complete remission. Among the six responding patients, the median remission was 17 months. Although four patients responded for more than 1 year, survival after VAD was similar for comparable patients who did or did not receive myeloablative treatment (P = .47) (Fig 2). Transplanted BM contained 11% to 20% plasma cells in five patients, among whom one patient responded for 16 months; with fewer plasma cells or with blood stem cell transplant, 5 of 10 patients responded (P = .26).

Consolidation of late remission. Eleven patients with resistant or relapsing disease responded to VAD and received myeloablative consolidation treatment at least 1 year after initial chemotherapy. Before VAD, the disease was unresponsive to standard therapy in three patients and had been relapsing in eight patients. Intensive therapy was given a median of 3 months after the onset of remission (range, 1 to 5 months), and there was one treatment-related death. Complete remission was confirmed in 4 of 10 patients with evaluable data in comparison with 1 of 14 control patients (P = .05); two additional transplanted patients showed greater than 75% decrease of residual tumor mass and four patients had less marked reductions. Low levels of normal IgM (<50 mg/dL) doubled to the normal range in three of six patients with evaluable data who received intensive therapy, in comparison with one of nine control patients (P = .10).
Among those who received myeloablative therapy, the median total remission time was 12 months, similar to the 7 months of comparable patients maintained on VAD ($P = .16$) (Fig 3). Only one transplanted patient responded for more than 2 years. In all patients with relapsing disease, the remission time after transplant was shorter than the first remission; survival after VAD was similar for comparable patients who did or did not receive intensive treatment ($P = .36$). Transplanted marrow contained less than 10% plasma cells in all patients.
and there was no relation between the degree of marrow plasmacytosis and outcome.

DISCUSSION

In recent years, myeloablative treatments supported by autologous BM or blood stem cells have been given to many patients with multiple myeloma. Regimens have varied and patients have been treated in different phases of disease, with the primary focus on the feasibility of the procedure and the frequency of remission. Myeloablative therapy with autologous transplant has been considered to be more effective in patients treated during the first year after diagnosis although controlled studies have not yet been conducted. The role of intensive therapy in patients later in the disease course has not been critically assessed. We examined the efficacy of this procedure in three groups of patients in late phases of disease who received two different, but similarly effective, myeloablative treatments. Patients were studied during resistant relapse, after at least 1 year of primary resistance, and during a VAD-induced remission of melphalan-resistant disease. Results were compared with those of similar patients who qualified for marrow transplantation in all respects but were denied treatment primarily for socioeconomic reasons. Because they continued to receive standard care, such patients appeared to provide a suitable comparison group for the patients who received intensive regimens. Their clinical features, response, and survival time were similar to those observed in previously reported trials with VAD for resistant myeloma. Undetected selection factors may have excluded some patients from either of our study groups, thereby biasing the outcomes; but we believe that such effects would have been small. The age, medical status, and tumor mass of the matched groups of patients were similar for each disease phase. This comparison provided some insight on the potential value of myeloablative therapy for patients in late phases of multiple myeloma.

Patients with myeloma in resistant relapse had a very poor outcome consistent with a previous report by Jagnanath et al. Whereas the myeloma was often sensitive to treatment, responses were brief and the survival short. The outcome was similar to that of comparable patients who were maintained on standard treatments until death. This experience was similar to the poor results observed in patients with large cell lymphoma during resistant relapse. One explanation for the initial sensitivity but early relapse could be the evolution with time of more resistant and proliferative subclones. Myeloma patients with relapsing disease have a higher growth fraction and greater numbers of colony-forming cells on in vitro culture studies, features that could explain the short remission and rapid tumor regrowth despite intensive therapy.

Patients with multiple myeloma and a long duration of primary resistance had a low response rate, approximately one half of that observed in similar patients who were treated during the first year of disease. This observation was consistent with an increase in the proportion of drug-resistant cells over time, similar to previous experiences with VAD treatment of melphalan-resistant myeloma. The increased resistance to intensive therapy was not explained by known prognostic factors, such as plasma cell hypodiploidy or high-serum lactate dehydrogenase. Whereas several
patients responded for more than 1 year and derived meaningful benefit, overall survival was not improved in comparison with control patients.

Myeloablative treatment supported by autologous BM or blood stem cells during late remission further reduced the myeloma, but remission and survival times were similar to those of control patients. Even when the disease was most limited before intensive treatment, recurrences occurred within 2 years in virtually all patients. Further study of intensive therapy should be reserved for patients earlier in their disease course, either for primary resistant disease or during a remission that is likely to be short after initial chemotherapy.

ACKNOWLEDGMENT

The authors thank Anita Kuo and Marie Sullivan for the analyses and Rose Guevara for excellent secretarial assistance.

REFERENCES

Limited value of myeloablative therapy for late multiple myeloma

R Alexanian, M Dimopoulos, T Smith, K Delasalle, B Barlogie and R Champlin