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 progenitor 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-doxorobucin 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.

IN RECENT YEARS, many patients with multiple myeloma resistant to standard therapies have received myeloablative treatment supported by autologous bone marrow (BM) or blood stem cell transplantation.[1-5] Because of the high risk of serious complications, such treatments have usually been limited to patients younger than 60, with good performance, and without serious medical complications. Most reports have included patients in diverse phases of disease, and none have compared results with those of similar patients who did not receive intensive therapy. Recent analyses have shown encouraging results in patients with primary resistant disease or in patients who have responded to initial chemotherapy.[2,5] Ablative regimens may be less useful during later phases of disease. In this report, we evaluate the results of myeloablative treatment supported by autologous BM or blood stem cells in specific categories of patients during late phases of multiple myeloma.

MATERIALS AND METHODS

Patients. Between January 1986 and April 1993, 49 patients with multiple myeloma received intensive, myeloablative therapy supported by autologous marrow or blood stem cells at least 1 year after initial chemotherapy. None were older than 62, had a Zubrod performance status other than 0 or 1, or had serious cardiac, pulmonary, or renal impairment. An age limit of 62 was chosen after treatment-related deaths occurred in four of five patients aged 63 to 69. The median age was 52, and key prognostic features are summarized in Table 1. All received intensive therapy after at least two courses of vincristine-doxorobucin by continuous infusion with pulse dexamethasone (VAD).[6] The myeloma was relapsing despite VAD in 23 patients (resistant relapse), was resistant to primary treatment for more than 1 year in 15 patients (prolonged primary resistance), and was consolidated during remission after successful VAD treatment of resistant disease in 11 patients (late remission).

From the University of Texas M.D. Anderson Cancer Center, Houston.

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Address reprint requests to Raymond Alexanian, MD, Box 1, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030.

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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 (140 mg/m^2) and total body irradiation (850 cGy TBI) as described previously[1]; thiotepa (750 mg/m^2) was substituted in five patients when intravenous melphalan was unavailable for 9 months; since 1991, a combination of thiotepa (750 mg/m^2), busulfan (10 mg/kg), and cyclophosphamide (120 mg/kg) was administered to 18 patients[3] (Table 1). 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 2×10^8 nucleated cells/kg and 1×10^4 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 2.5×10^8 nucleated cells/kg and 3×10^6 CD34$^+$ mononuclear cells/kg. All patients received prophylactic antibiotics, initially trimethoprim, sulfamethoxazale, 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.[1-3] All responding patients were maintained on interferon-α (1 to 2 million units/m^2, three times weekly) with dexamethasone (20 mg/m^2 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.[7,8] 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%.[9] 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; 31 additional patients (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,

Table 1. Clinical Features of Patients Who Received Myeloablative or Standard Therapy

	Resistant Relapse		Primary Resistance		Late Remission	
	Transplant	Control	Transplant	Control	Transplant	Control
No. patients	23	33	15	32	11	14
Median age (range)	52 (38 - 61)	52 (30 - 62)	52 (41 - 62)	55 (22 - 62)	50 (43 - 62)	49 (30 - 62)
Pre-VAD status						
Tumor mass						
High	4	7	0	0	0	0
Intermediate	4	10	9	18	3	6
Low	15	16	6	14	8	8
B_2M (mg/L)						
(median and range)	3.1 (1.3 - 35)	3.6 (1.9 - 14)	2.8 (1.6 - 8.8)	3.3 (1.4 - 6.7)	2.6 (1.7 - 6.5)	3.5 (2.2 - 6.4)
Median months						
1st therapy—transplant	29	—	18	—	34	—
1st therapy—VAD	20	37	8	10	27	42
Ablative therapy						
Melphalan-TBI	14	—	8	—	4	—
Thiotepa-TBI	1	—	0	—	4	—
TBC	8	—	7	—	3	—
Stem cell source						
Marrow	23	—	11	—	10	—
Blood	0	—	4	—	1	—

Abbreviations: B_2M, Beta$_2$microglobulin; TBC, Thiotepa busulfan cyclophosphamide.

and would have received a transplant-supported treatment if that procedure had been possible. Only patients who lived at least 3 months after VAD were included, because that was the minimum interval between VAD and intensive therapy. All patients who met the criteria for control patients were included for comparison with the 49 transplanted patients. Because the disease stage was low or intermediate before VAD for those who received intensive therapy for primary resistant disease or during late remission, controls in these categories were limited to those with the same disease stages. For each treatment group, age and major prognostic factors were similar for patients who received a transplant-supported treatment or were continued on VAD (Table 1).

Statistical analysis. The Kaplan-Meier method was used to calculate survival and remission distributions, and differences were compared by a Wilcoxon test. Survival was measured from the initiation of intensive therapy, and from the onset of VAD therapy for comparisons between transplant and control groups. Remission time was calculated from the onset of a 75% reduction of myeloma protein synthesis to the first objective sign of relapse.

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).

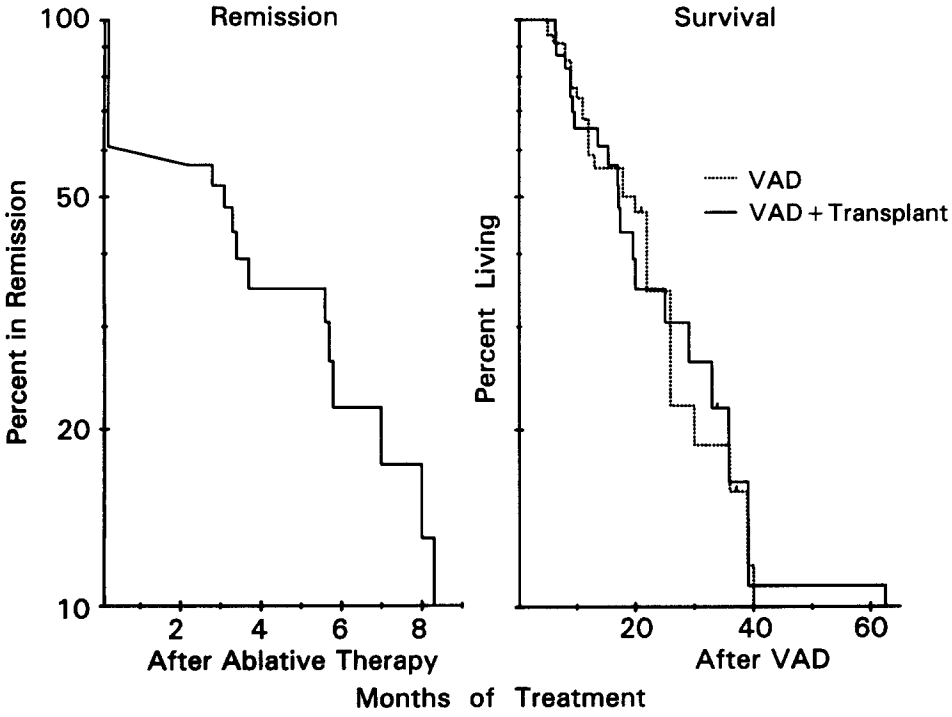

Fig 1. (Left) Remission time of 23 patients with relapsing disease after myeloablative therapy. (Right) Survival after VAD of transplanted and 33 control patients.

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

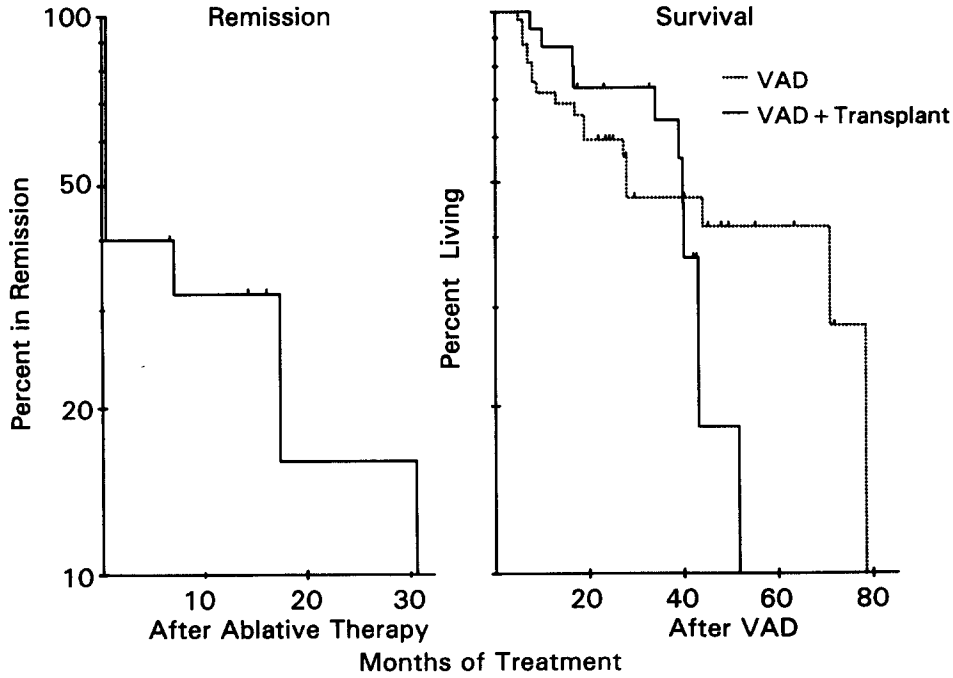

Fig 2. (Left) Remission time of 15 patients with primary resistant myeloma after myeloablative therapy. (Right) Survival after VAD of transplanted and 32 control patients.

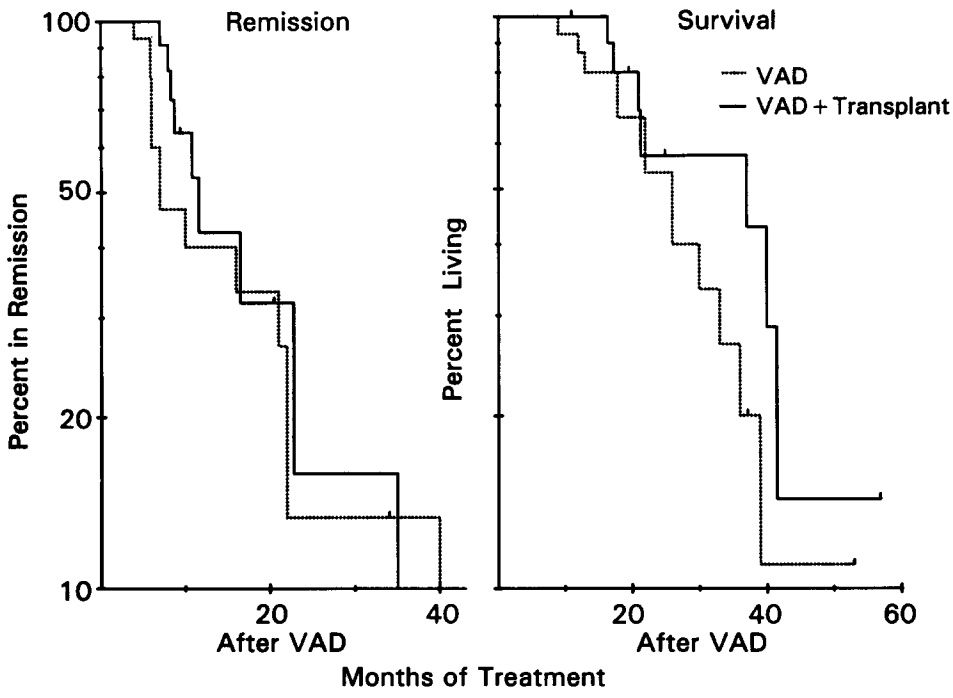

Fig 3. (Left) Remission times of 11 patients after a sequence of VAD salvage and myeloablative therapies, and of 15 control patients. (Right) Survival after VAD of same groups of patients.

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.[1-5] 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.[2,4,5] 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.[1,3] 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.[6,10,11] 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 Jagannath et al.[2] 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.[12] One explanation for the initial sensitivity but early relapse could be the evolution with time of more resistant and proliferative subclones.[13] Myeloma patients with relapsing disease have a higher growth fraction and greater numbers of colony-forming cells on in vitro culture studies,[14,15] 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,[12,13] similar to previous experiences with VAD treatment of melphalan-resistant myeloma.[6] The increased resistance to intensive therapy was not explained by known prognostic factors, such as plasma cell hypodiploidy or high-serum lactate dehydrogenase.[16,17] 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. Thus, myeloablative treatment using mixtures of current drugs, or with total body irradiation, was helpful to very few patients during late phases of multiple myeloma. 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.[17]

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