# Early Myeloablative Therapy for Multiple Myeloma

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**The value of early myeloablative therapy supported by autologous bone marrow or blood progenitor cells was assessed in 72 patients with multiple myeloma who were treated within 1 year of initial therapy. Forty-five patients were consolidated during remission, and 27 patients were treated for primary refractory disease. Outcomes were compared with those of similar patients who did not receive intensive treatment primarily for socioeconomic reasons. Among patients who had responded previously, myeloablative therapy increased the rate of complete remission from 5% to 45% ($P < .01$) but did not prolong progression-free intervals or survival times. The same treatment controlled the myeloma in 70% of patients with primary resistant disease and prolonged the median survival from 37 to 83 months ($P = .03$). Intensive treatment for primary resistant myeloma administered later in the disease course resulted in significantly lower response rates and shorter progression-free intervals. Current myeloablative regimens supported by autologous stem cells appeared useful primarily in patients with primary resistant disease during the first year of therapy.**



IN RECENT YEARS, many patients with multiple myeloma (MM) who were responsive or resistant to initial standard therapies have received myeloablative treatment supported by autologous bone marrow (BM) and/or blood stem cell transplantation.[1-7] Because of the high frequency of serious toxicity, only patients younger than 60, with good performance, and without other serious diseases have usually been considered for such treatments. Most reports have combined patients in diverse phases of MM, and few have compared results with those of control patients who received standard dose therapy. Results in several series appeared encouraging for patients treated during early phases of disease,[3-5] but little value has been observed during later stages.[7] In this report, we evaluate the results of myeloablative treatment supported by autologous BM or blood stem cells during the first year of therapy.

## MATERIALS AND METHODS

*Patients.* Between 1985 and 1994, 72 patients with MM received intensive, myeloablative therapy supported by autologous BM or blood stem cells within 1 year after the start of chemotherapy. All patients were ≤ 60 years old, 87% had a Zubrod performance of 0 or 1, and none showed serious cardiac, pulmonary, or renal impairment. The median age was 48, and patient characteristics are summarized in Table 1. All received intensive therapy after at least 2 courses of vincristine-doxorubicin by continuous infusion with pulse dexamethasone (VAD; 24 patients), pulse dexamethasone alone (19 patients), or a high-dose cyclophosphamide-etoposide combination (29 patients).[8-10]

The myeloma was treated during remission in 45 patients and while resistant and stable in 27 patients. Patients with low tumor mass that had responded were not eligible for intensive therapy to avoid serious complications among patients with a good prognosis, but patients with all stages of primary resistant myeloma were eligible.

*Treatment.* Myeloablative treatment for 24 patients consisted of a combination of melphalan (140 mg/m$^2$) and total body irradiation (TBI; 850 cGy) as described previously[1]; thiotepa was substituted in 5 patients when intravenous melphalan was unavailable. Since 1991, a combination of thiotepa (750 mg/m$^2$), busulfan (10 mg/kg), and cyclophosphamide (120 mg/kg) was administered to 43 patients (see Table 1).[6] 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 for 43 patients consisted of at least $2 \times 10^8$ nucleated cells/kg and $1 \times 10^4$ granuloyte-macrophage colony-forming units (CFU-GM)/kg; blood stem cells were administered to 29 recent patients (usually because of BM plasmacytosis greater than 20% or an inadequate BM harvest) and consisted of at least $2.5 \times 10^8$ nucleated cells/kg and $2 \times 10^6$ CD34$^+$ mononuclear cells/kg. Previous reports have described the times to granulocyte and platelet recovery, the toxicity, and the treatment-related complications.[1,6] Provided a disease response had been sustained or achieved, both transplanted and control patients received the same maintenance and rescue treatments until death. These consisted of initial maintenance with $\alpha$-interferon (2 million U/m$^2$ 3 times weekly; 1986 to 1990) or interferon with dexamethasone 20 mg/m$^2$/d for 4 days each month (1990 to present), followed by sequential melphalan-prednisone and VAD treatments for relapsing disease.

*Staging and response.* Plasma cell tumor mass was defined in each patient as high, intermediate, or low by standard criteria.[11,12] High tumor mass required either hemoglobin less than 8.5 g/dL or serum calcium greater than 11.5 mg/dL; intermediate tumor mass was defined by hemoglobin between 8.5 to 10.5 g/dL or serum myeloma protein greater than 4.5 g/dL with normal serum calcium; low tumor mass required both hemoglobin 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 BM plasmacytosis to less than 5%.[13] Complete response required disappearance of serum myeloma protein by immunofixation.

*Control patients.* For each of the 2 disease phases under study, control patients were identified who were responsive or resistant to the same primary therapies and met the eligibility criteria for myeloablative therapy, but did not receive such treatment. Patients either refused intensive treatment, were denied coverage of the procedure by their insurance company, were ineligible for TBI because of prior radiotherapy to the spine, or received VAD without subsequent transplantation during the 3 years before activation of the transplant protocol. As in patients who received intensive therapy, control patients were 60 years old or less; had an acceptable performance; were free of serious cardiac, pulmonary, or renal dysfunction; and would have received a transplant-supported treatment if that procedure had been possible. Control patients with resistant and

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

| | First Remission | | Primary Resistance | | |
|---|---|---|---|---|---|
| | Transplant (range) | Control (range) | Early Transplant (range) | Control (range) | Late Transplant (range) |
| No. of patients | 45 | 31 | 27 | 60 | 14 |
| Median age | 49 (32-60) | 51 (25-59) | 45 (20-60) | 55 (22-60) | 51 (14-60) |
| Pretherapy status* | | | | | |
| Tumor mass | | | | | |
| High | 25 | 12 | 7 | 11 | 0 |
| Intermediate | 20 | 19 | 11 | 18 | 9 |
| Low | — | — | 9 | 31 | 5 |
| Median $B_2M$ (mg/L) | 4.9 (2.1-14.9) | 4.2 (1.6-14.4) | 2.8 (1.5-7.9) | 3.2 (1.0-7.2) | 2.7 (1.6-7.8) |
| Median months | | | | | |
| 1st therapy-transplant | 6.3 (1.1-11.8) | — | 5.2 (3.0-11.9) | — | 18.2 (13.8-27.5) |
| Ablative therapy | | | | | |
| Melphalan-TBI | 15 | — | 9 | — | 7 |
| Thiotepa-TBI | 4 | — | 1 | — | 0 |
| T-B-C | 26 | — | 17 | — | 7 |
| Stem cell source | | | | | |
| BM | 30 | — | 13 | — | 10 |
| Blood | 15 | — | 14 | — | 4 |

Abbreviation: T-B-C, thiotepa-busulfan-cyclophosphamide.

*Before initial therapy for patients treated during first remission or for early resistant disease and before VAD rescue for patients treated for late resistant disease.

stable disease were required to have lived at least 3 months after primary treatment because that was the minimum interval between primary and intensive therapies (Table 1). Because the disease stage was high or intermediate before initial therapy for those consolidated during remission, control patients in this category were selected with the same disease stages. Because the serum $\beta_2$microglobulin ($\beta_2M$) level was less than 15.0 mg/L in all patients transplanted during remission and less than 8.0 mg/L in those transplanted for resistant disease, control patients in each category also had a lower value. For each treatment group, age and major prognostic factors were similar for patients who received a transplant-supported treatment or were continued on standard treatment (Table 1).

*Statistical analysis.* The Kaplan-Meier method was used to calculate survival and remission times, and differences were compared by the Wilcoxon test. Survival was measured from initial therapy for comparisons between transplanted and control groups. Progression-free intervals were calculated from a 75% reduction of myeloma protein synthesis to the first objective sign of relapse despite VAD.

## RESULTS

*Remission consolidation.* A complete response had been achieved with initial therapy in 5% of responding patients destined to receive myeloablative treatment and in 7% of similar patients who were maintained on standard therapy; after intensive treatment, a complete response was induced in 40% more patients who survived the procedure for an overall frequency of 45% ($P < .01$). A complete response was confirmed after a median of 2 months after myeloablative treatment (range, 1 to 8 months) and occurred in 69% of those with a serum myeloma protein of 0.6 g/dL or less in contrast to 24% of patients with a higher value ($P < .01$).

Treatment-related deaths occurred in 5 patients (11%) who received myeloablative treatment but in no control patient ($P < .01$). Of 5 patients who died, 4 were at least 55 years old, so that an early death occurred in 29% of older patients and in 3% of younger patients ($P = .01$). Survival and progression-free intervals were similar for patients who received intensive or standard therapies that included comparisons of progression-free interval beyond 2 years; the outcomes were similar even for comparable patients less than 55 years old (see Fig 1).

*Primary resistance less than 1 year.* Among 27 patients with primary resistant disease for less than 1 year who received myeloablative treatment, 1 patient died of toxicity (4%), and 19 patients responded (70%) including 2 patients with a complete remission (8%). The response rate was slightly higher among patients with low tumor mass at diagnosis than among those with more advanced disease ($P = .14$; see Fig 2), but similar for patients with less than a 50% reduction or a 50% to 74% reduction of the myeloma after standard treatment. Survival from primary therapy was significantly longer among patients who received myeloablative therapy than among comparable patients who remained resistant to standard therapies ($P = .03$; see Fig 3). Only among the patients with high or intermediate tumor mass at diagnosis was there a significant difference in survival.

The outcome of the 19 patients with primary resistant disease who then responded to myeloablative therapy (later remission) was compared with that of 61 control patients of similar age, and with similar disease stage and $\beta_2M$ who had responded to standard therapies without transplantation (primary remission). The median survival of approximately

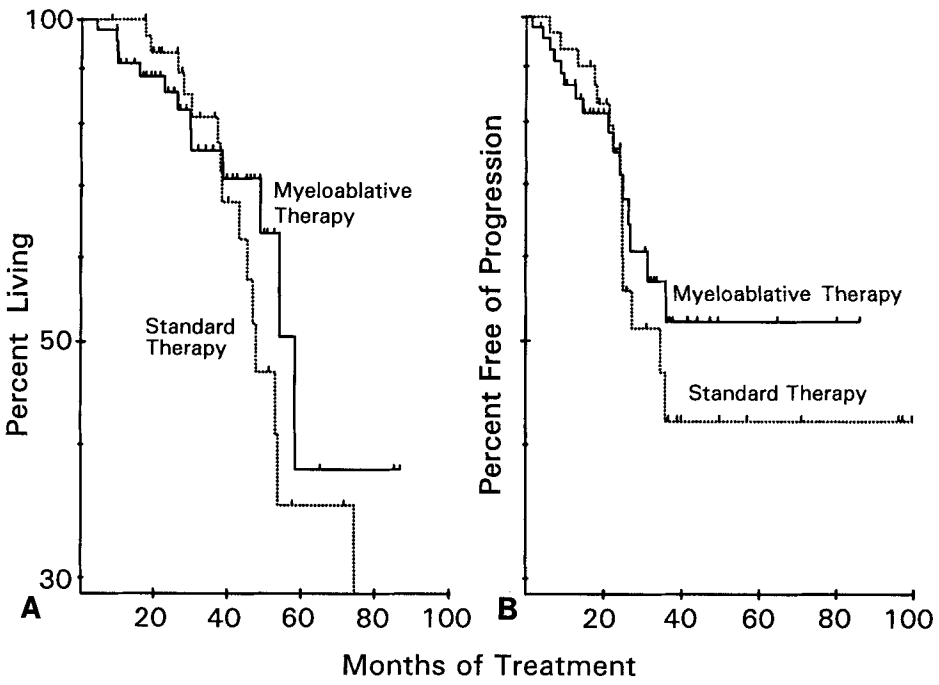


**Fig 1. (A) Similar survival is shown from primary treatment of 45 responding patients who received myeloablative consolidation therapy and of 31 control patients. (B) Similar progression-free intervals are shown of same groups of patients.**

6 years and progression-free interval of approximately 3.5 years were similar for both groups of patients.

*Duration of primary resistance.* The outcome of patients with primary resistant and stable disease who received intensive treatment within 1 year was compared with those of 14 similar patients who received an identical treatment later.[7] Patient groups were matched for age, disease stage, contemporary time period, and prior therapies, except that no patient with high tumor mass received late intensive treatment (Table 1). The response rate decreased progressively as the interval lengthened between initial and myeloablative treatment ($P$ = .02 by linear trend analysis; see Fig 2). In addition, the progression-free interval was significantly shorter among patients responding to later therapy ($P$ = .03; see Fig 3).

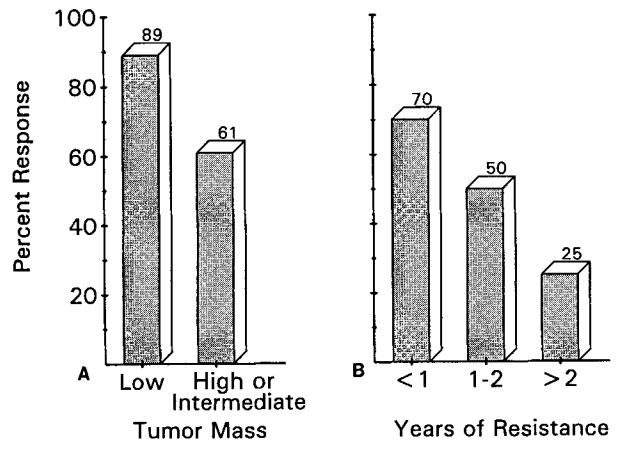


**Fig 2. (A) Response rates are shown of patients with primary resistant disease who received myeloablative therapy during the first year. (B) Lower response rates are shown of similar patients with later treatment.**

## DISCUSSION

Myeloablative treatments supported by autologous BM or blood stem cells have been assessed in many patients with MM.[1-7] Regimens have varied but the results have been similar with combinations of alkylating agent-TBI or with busulfan-cyclophosphamide regimens.[6] Disease stage and the interval from diagnosis to transplantation are important prognostic variables,[3] and a recent analysis showed little value of myeloablative treatment for most patients treated late in their course.[7] Better results have been claimed for patients treated during the first year,[3-5] but no controlled studies have been published. We studied the efficacy of this procedure during the first year in 2 groups of patients, namely those with disease that was either responsive or resistant to programs such as VAD.[8-10] Results were compared with those of control patients who were matched for major prognostic variables and qualified for autologous cell transplantation in all respects but were denied treatment primarily for socioeconomic reasons. Because they continued to receive standard care, such patients were considered to represent a suitable control group for patients who received intensive treatment. Undetected selection factors may have excluded some patients from either group, perhaps biasing the outcomes, but we believe that such effects would have been small.

Although the survival of all patients who received myeloablative treatment was significantly longer than that of control patients ($P$ = .03), the results differed according to the disease status before treatment. The outcome of patients

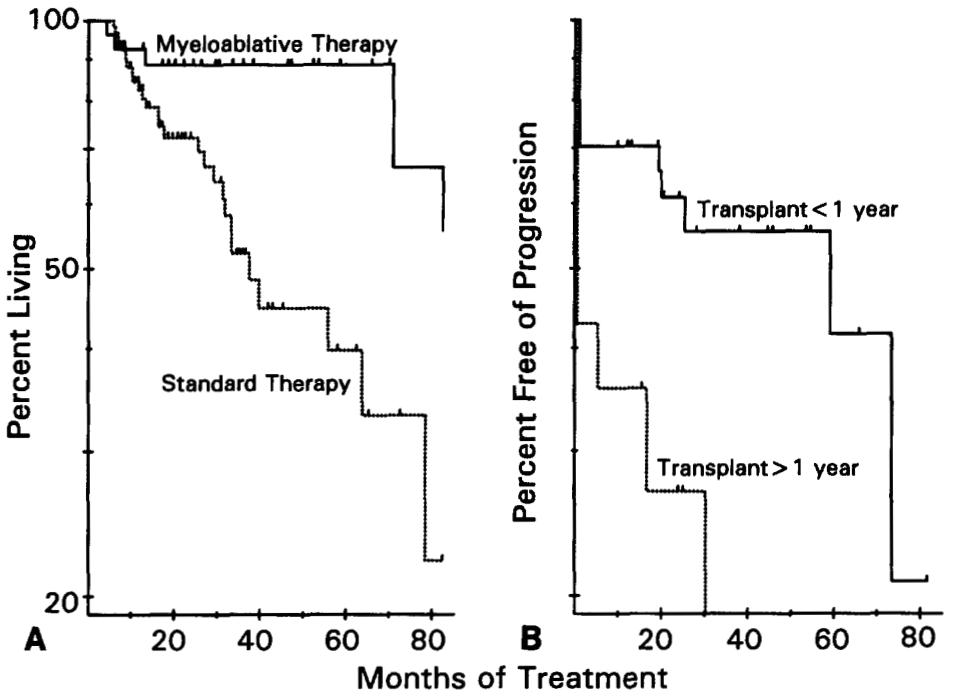


**Fig 3. (A) Longer survival from primary treatment is shown for 27 patients with resistant disease who received early myeloablative therapy than that for 60 control patients ($P = .03$). (B) Longer progression-free intervals are shown for 19 patients who responded to myeloablative therapy within 1 year than those for 6 patients who responded to later treatment ($P = .03$).**

who received intensive consolidation treatment of responsive disease was similar to that of patients who continued standard therapy. The significantly higher rate of complete remission with myeloablative therapy was consistent with the reports of others,[2-5] but this occurrence was associated with a median progression-free interval and survival no more than 6 months longer than those observed in other responders. The potential gain from a more marked tumor reduction of modest duration in some patients was balanced by the treatment-related mortality in others. Consequently, the overall survival was similar to those of a matched, control population who received the same maintenance and rescue treatments during their lifetime. Our findings do not support the use of currently available myeloablative treatments for advanced MM that has responded to chemotherapy, and new regimens are needed for this category of patients. Because our trial of intensive consolidation therapy excluded patients with less advanced disease who may be more likely to benefit, further study may be useful for patients in this category. The high rate of complete response among transplanted patients also justifies the study of innovative strategies that may delay relapse after transplantation, such as with immunologic or biologic therapies. Recently, $\alpha$-interferon was reported to improve the median progression-free survival of transplanted patients by 12 months (in comparison with no maintenance treatment), and the benefit appeared longer in patients with a complete response.[14] Another uncertainty is whether malignant cells in the autologous transplant contribute to relapse and whether stem cell selection or purging techniques prolong the progression-free interval.

On the other hand, early myeloablative therapy benefited patients with stable disease resistant to initial treatment when the prognosis with continued ineffective therapy was limited. This applied primarily to patients with advanced disease at diagnosis for whom the survival was otherwise short. For patients without serious medical problems, the high response rate and long survival justify intensive therapy even with a projected mortality of approximately 10%. This favorable outcome resembled that observed in many patients who received intensive therapy for stable or partially responsive large cell lymphoma.[15] Of major interest were the similarly long progression-free interval and survival after successful myeloablative therapy of resistant myeloma and standard therapy of newly diagnosed disease. Thus, the differences between "resistant" and "sensitive" disease appeared to be sufficiently small that the apparent tumor resistance could be overcome with higher doses of effective drugs. The long progression-free interval also argued against the presence in most patients of aggressive tumor subclones during the first year that might have caused early relapse, as appeared to be present in patients treated for relapsing disease several years later.[7]

When the primary resistant disease was more advanced or treated later in the disease course, the response rate was less, and the progression-free interval was shorter. This observation was consistent with an increase of the proportion of drug resistant cells with progressive disease and/or a higher proliferative rate with time,[16] similar to our previous experiences with VAD or dexamethasone treatment of melphalan-resistant myeloma.[17] Thus, patients with resistant and stable myeloma should be identified early for high-dose therapy to have the best chance for remission, to collect blood progenitor cells before their numbers are compromised by prolonged therapy, and to prevent serious complications from myeloma that would contraindicate the procedure. Several European groups have described the results of similar myeloablative

treatments supported by autologous stem cells for selected patients treated during early phases of MM.[2,4,5] Despite different treatments and criteria for eligibility and response, there were similar treatment-related mortalities (3% to 15%), a high rate of overall and complete response (28% to 50%), but no substantial prolongation of survival (median, 37 to 40 months) in comparison with the projected outcome of similar patients who received standard therapies.[8,9] A preliminary report has described longer progression-free and survival times among patients randomized to myeloablative treatment than to continued standard treatment.[18] Our studies suggested that meaningful benefit was limited primarily to patients with primary resistant and stable disease. When analyses include a mixture of patients with responsive and resistant disease, with different extents of disease, and with varying durations before intensive treatment, the benefits derived by specific subgroups may be difficult to recognize. Controlled trials should clarify more definitively the role of myeloablative therapy with autologous stem cell transplantation for specific groups of patients with MM.

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