Myeloablative Therapy for Primary Resistant Multiple Myeloma

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Abstract. Myeloablative therapy supported by autologous bone marrow or blood stem cell transplantation was assessed in 41 patients who had multiple myeloma resistant to vincristine-doxorubicin by continuous infusion with high-dose dexamethasone (VAD) or other high-dose dexamethasone regimens. In patients who had high or intermediate tumor mass, the myeloma cell mass was reduced by more than 75% in 56% of patients and the survival time quadrupled in comparison with that of a matched control group. Later treatment resulted in a lower response rate and shorter remission. Current myeloablative regimens supported by autologous stem cells provided a useful treatment for patients who had advanced primary resistant multiple myeloma. Such treatment should be given early in the disease course to provide the best chance for remission, collecting blood stem cells with facility, and preventing complications that would increase the risk of the procedure.

Introduction

Few effective treatments are available for patients who have multiple myeloma that is resistant to both alkylating agents and VAD. Several regimens of high-dose alkylating agents have induced remissions in approximately one-third of such patients, but the morbidity rate has been high and the remission duration short [1, 2]. Myeloablative treatment supported by autologous bone marrow and/or blood stem cell transplantation has resulted in higher response rates, but few studies have tried to identify the patients most likely to benefit from the treatment [3-6]. In this report, we evaluate the results of myeloablative treatment for primary resistant multiple myeloma and compare the results with those observed after continued standard treatment.

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Materials and Methods

Between 1985 and 1993, 41 patients who had primary resistant multiple myeloma received intensive myeloablative therapy supported by autologous bone marrow or blood stem cells. None had responded to previous VAD, high-dose dexamethasone, or high-dose cyclophosphamide-etoposide therapy when response was defined as a 75% or greater reduction of serum myeloma protein production, a 95% or greater reduction of Bence Jones protein and a reduction of marrow plasmacytosis to less than 5% [7]. All patients were ≤62 years old (median 48), showed good performance and did not have a serious cardiac, pulmonary or renal disease. Plasma cell tumor mass was defined by standard criteria [8], and patients were grouped according to whether myeloablative treatment was given after less than or more than one year of standard chemotherapy (Table I).

Treatment

Myeloablative treatment consisted of a combination of high-dose melphalan and total body irradiation for 17 patients [3], or a combination of high-dose thiotepa, busulfan and cyclophosphamide for 24 patients [9]. Within 48 h of the completion of therapy, patients received either autologous bone marrow ($>1.0 \times 10^4$ colony-forming units/kg) or blood stem cells ($>2.0 \times 10^6$ $CD34^+$ cells/kg). All responding patients were maintained on a combination of interferon

Table I. Clinical features of patients with primary resistant myeloma who received myeloablative or standard therapy

	Early Transplant	Control	Late Transplant	Control
No. patients	25	22	16	39
Median age (range)	45 (20-55)	50 (38-55)	53 (41-62)	55 (22-62)
Protherapy status				
Tumor mass				
High	6	3	0	0
Intermediate	11	10	9	18
Low	8	9	7	21
B_2M (mg/l) (median and range)	2.8 (1.5-6.6)	3.3 (2.0-4.4)	2.7 (1.6-8.8)	3.3 (1.7-8.3)
Median months from first therapy-transplant (range)	4.3 (3.0-10.7)	– –	18.0 (12.0-27.5)	– –

(3×10^6 units subcutaneously 3 × weekly) and dexamethasone (20 mg/m^2 each morning for four consecutive days each month).

Control Patients

Control patients were resistant to the same primary therapies but were denied intensive treatment primarily for socioeconomic reasons; they were of similar age, with good performance and would have received myeloablative treatment if possible (Table I). Because the minimum interval between primary and intensive therapies was three months, all control patients lived at least three months after primary treatment. Major prognostic factors were similar for patients who received a transplant-supported treatment or who continued standard treatment (Table I).

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, and remission was calculated from the interval between a 75% reduction of myeloma protein synthesis and the first sign of relapse.

Results

Primary Resistance <1 Year

Among 25 patients who had myeloablative treatment for primary resistant disease within one year, 17 patients responded (68%), including six patients who had a complete remission; one patient died of toxicity. The response rate was higher among patients with low tumor mass at diagnosis than among those with more advanced disease ($p = 0.09$) (Fig. 1).

Survival from primary therapy was longer among patients who had high or intermediate tumor mass and received myeloablative therapy than among control patients who remained resistant to continued standard therapies ($p < 0.01$) (Fig. 2). The difference remained marked even when patients transplanted later were included in the control group and their survival was censored at the time of transplantation ($p = 0.03$). No gain

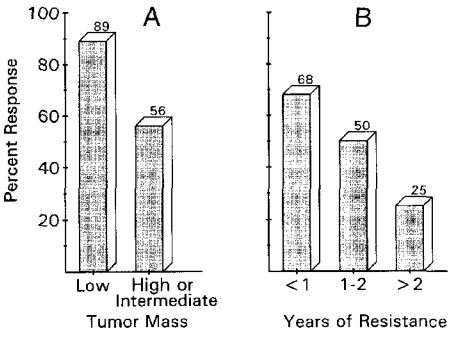

Fig. 1. Panel A: Response rates of patients with different tumor mass who received intensive therapy for primary resistant disease within one year. Panel B: Response rates of patients with primary resistant disease treated after different durations of standard therapy.

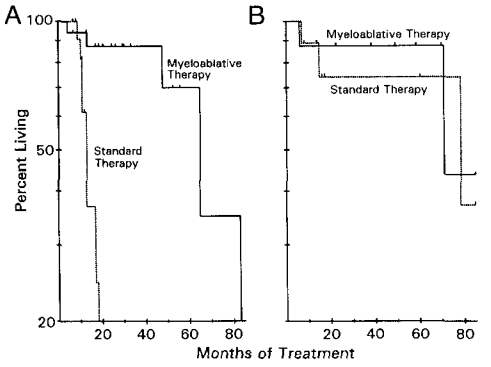

Fig. 2. Panel A: Longer survival from initial therapy of patients who had myeloma of high or intermediate tumor mass at diagnosis and received myeloablative therapy within one year in comparison with control patients who continued standard therapy ($p < 0.01$). Panel B: Similar survival for treated and control patients who had myeloma of low tumor mass.

was evident for the small number of patients who had low tumor mass compared with control patients (Fig. 2).

The survival of the 17 patients who had primary resistant disease and responded to early myeloablative therapy was compared with that of 52 control patients who responded to standard therapies (primary remission). The median survival and remission times were similar for both groups (Fig. 3).

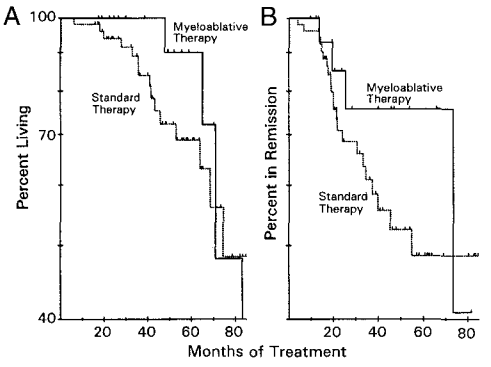

Fig. 3. Panel A: Similar survival of comparable patients who had primary resistant disease that responded to myeloablative therapy and of newly diagnosed patients who responded to standard therapy. Panel B: Remission times for the same groups of patients.

Primary Resistance >1 Year

Among 16 patients who had primary resistant myeloma for more than one year and who received the same myeloablative treatment, seven patients responded (44%), none of whom achieved a complete remission; two patients died of toxicity. As indicated in Figure 1, the response rate fell progressively as the interval lengthened between initial and myeloablative treatment ($p = 0.03$ by linear trend analysis). The median remission of approximately two years for the seven patients who responded to later therapy was shorter than that of approximately six years for the 17 patients who responded to earlier intensive treatment ($p = 0.14$). Despite this difference, the overall survival was similar for patients who received later myeloablative therapy and those who continued standard treatment [10].

Discussion

Many patients who have multiple myeloma resistant to standard chemotherapy have received myeloablative treatments supported by autologous bone marrow or blood stem cells [3-6]. To justify a procedure that causes frequent morbidity, eligibility has usually been restricted to patients with clear resistance to a VAD-based program [2]. Myeloablative regimens have varied, but the outcomes have been similar for melphalan-total body irradiation and busulfan-cyclophosphamide-thiotepa regimens [9]. We studied the utility of myeloablative therapy in patients who had primary resistant disease for more than or less than one year, comparing the results with those for control patients who had similar prognostic factors but were denied intensive treatment.

Early myeloablative therapy benefited most patients who had primary resistant disease when the prognosis with continued ineffective therapy was limited. Among patients 62 years old or less who had advanced disease, the response rate of 56% and the marked prolongation of survival appeared to justify the early mortality rate of 8%. For older patients or those with impaired performance and/or organ function, the risks are likely to be higher and a careful review of the risk-benefit ratio is necessary. No gain was apparent for patients who had low tumor mass. Our favorable outcome for most patients resembled that observed for patients given intensive therapy for stable or partially responsive large

cell lymphoma [11] and justifies similar trials in patients who have low grade B-cell lymphomas.

Remission and survival times were similar for comparable patients who responded to intensive therapy for resistant disease or to standard therapy for newly diagnosed disease. Because the apparent tumor resistance was overcome by higher doses of effective drugs, the differences between "resistant" and "sensitive" disease appeared to be small. The long remission time for patients treated effectively within the first year indicated that aggressive tumor subclones that might have caused early relapse were absent in most patients, in contrast to their dominance in patients who have later relapsing disease [10].

When primary resistant myeloma was treated later, the frequency of response was less and the remission shorter. These findings were compatible with an increasing fraction of drug-resistant cells with time, as observed previously with VAD or dexamethasone treatment of melphalan-resistant myeloma [12, 13]. Thus, early intensive treatment of primary resistant myeloma provides the best chance for achieving remission, collecting blood stem cells before their yield is reduced by therapy and before encountering disabling complications that contraindicate the procedure.

Acknowledgments

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