

High-Dose Chemoradiotherapy and Autologous Bone Marrow Transplantation for Resistant Multiple Myeloma

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Seven patients with advanced multiple myeloma, refractory to therapy with alkylating agent-VAD (vincristine-adriamycin-dexamethasone), received a regimen combining high-dose melphalan with total body irradiation supported by autologous bone marrow transplantation. Very rapid, usually >90% tumor mass reduction was achieved in six patients, regardless of prior chemotherapy responsiveness and marrow plasmacytosis up to 30%. Despite signs of early relapse in three patients (median

remission duration of all patients, 15 months), five remain alive and well without further cytotoxic therapy from 2 to 21 months (median, 9+ months). Two patients died, one from surgical complications after transplantation and a second due to persistent neutropenia with fatal pneumonia. This treatment provides meaningful disease control for selected patients with resistant myeloma and a poor prognosis.

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FOR NEARLY 20 years, the combination of melphalan and prednisone (MP) has been the standard therapy for multiple myeloma. Once resistance to treatment develops, other agents have been ineffective, and survival has been short. Using a program that combines a continuous infusion of vincristine and adriamycin with dexamethasone (VAD), about 50% of patients resistant to MP responded, but for a median duration of only 9 months.^{1,2} Despite encouraging results with high-dose melphalan (HDM) in untreated myeloma,^{3,4} the median duration of remission in patients resistant to VAD was only 3 months.⁵ Since autologous bone marrow transplantation (BMT) improved the tolerance to HDM,⁵ we added total body irradiation (TBI) to the cytoreductive program^{5a} in an attempt to achieve more frequent and durable remissions in a tumor generally acknowledged to be radiosensitive. While there is only limited experience with TBI alone in myeloma,⁶ extramedullary plasmacytomas are dependably eradicated with total doses of 4500 cGy,⁷ and local manifestations of advanced myeloma are effectively palliated even with single doses of 700 to 1000 cGy.^{8,9}

We now report our initial experience with TBI and HDM in conjunction with autologous BMT in seven consecutive patients with VAD-refractory myeloma. Six patients have responded with >75% tumor mass reduction for a median of 15 months; and five patients remain alive from 2 to 21 months. Incidence and duration of remission were independent of prior chemotherapy resistance and not influenced by the degree of plasmacytosis in the marrow autografts.

MATERIALS AND METHODS

Seven consecutive patients with advanced multiple myeloma resistant to prior standard treatments and VAD form the basis of this report (Table 1). Their ages ranged from 45 to 63 years (median, 50 years). Written informed consent was obtained from all patients prior to therapy, indicating its potential benefits and risks, in keeping with institutional policy. Three patients were unresponsive to initial alkylating agent and VAD therapy, and one patient (ES) had not even responded to HDM at a dose of 70 mg/M²; four were relapsing despite VAD. Tumor mass was high in four patients and intermediate in two; myeloma protein type was IgA in three and IgG in three; one patient had nonsecretory myeloma with 27% plasmacytosis (patient JH). Four patients were moderately disabled from painful lumbar spine compression fractures, and one patient was bedridden from fractures of femur and humerus, with hypercalcemia and progressive skull plasmacytomas (Table 1, patient BL).

Except for the one bedridden patient who required intensive nursing, treatment was given in a protected environment unit and consisted of TBI in a dose of 850 cGy in five fractions over 2½ days, preceded (two patients, FS and GR, Table 1), or followed one day later by melphalan 140 mg/M² intravenously (IV) over 30 minutes (remaining five patients). Bone marrow was infused on the following day in a dose of at least 2×10^8 nucleated cells per kilogram body weight. Autologous marrow had been harvested during a previous VAD-induced remission in three patients (marrow plasmacytosis of 6%, 6%, and 11%) and after resistance to initial or salvage alkylating agent-VAD treatment in four patients (6%, 10%, 27%, and 30% plasmacytosis). Antibiotic prophylaxis was performed with trimethoprim sulfamethoxazole and ketoconazole. Additional supportive care was given as needed, including blood products and IV broad spectrum antibiotics. Frequent measurements of myeloma protein level were conducted, and clinical response was defined by a greater than 75% reduction in calculated tumor mass.¹⁰ Bone marrow aspirates and biopsies were examined morphologically and by flow cytometry to determine abnormalities in DNA and RNA content and to monitor the proportion of cells with monoclonal cytoplasmic immunoglobulin light chain expression.^{11,12} This technique has consistently detected <1% monoclonal plasma cells.

RESULTS

All six patients with measurable myeloma protein responded rapidly to treatment with a median tumor halving time of 12 days, and ≥90% tumor mass reduction was achieved in four patients (Table 1, Fig 1). Marrow plasmacytosis cleared in all seven patients, including two whose

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Table 1. Patient Characteristics and Response to TBI/High Dose Melphalan

Patient	Age (yr)	Months from Diagnosis	No. of Prior Responses	Tumor* Mass	Performance† Status	Tumor Cells in Marrow		Response			Current Status				
						Autograft (%)‡	Tumor Reduction (%)	Tumor Halving (d)	Relapse- Free (mo)	Survival (mo)	Tumor Cells in Bone Marrow (%)‡	Hemoglobin (g/dL)	Granulocytes (× 10 ³ /μL)	Platelets (× 10 ³ /μL)	Back to Work
FS	46	4	0	I	2	30	93	12	21+	21+	<1	13.1	2.5	295	Yes
GR	50	106	3	H	2	6	99	9	15	17+	<1	14.3	2.9	171	Yes
LQ	51	6	0	I	0	10	78	12	11+	11+	<1	14.4	3.1	321	Yes
RS	45	27	1	H	0	6	90	12	6	8+	3	12.3	4.0	300	Yes
BL	59	31	1	H	4	11	97	10	3	3	<1	11.0	2.5	48	Dead, 3.0 mo
JH	50	39	1	H	0	27	<1% PC§	—	—	2.5	<1	11.7	0.7	10	Dead, 2.5 mo
ES	63	27	0	I	0	6	90	8	2+	2+	<1	10.3	3.5	165	Yes

*Tumor mass: I, intermediate; H, high (Durie-Salmon).

†Performance status, Zubrod scale.

‡Using DNA-Cig flow cytometry.

§Plasma cells, nonsecretory myeloma.

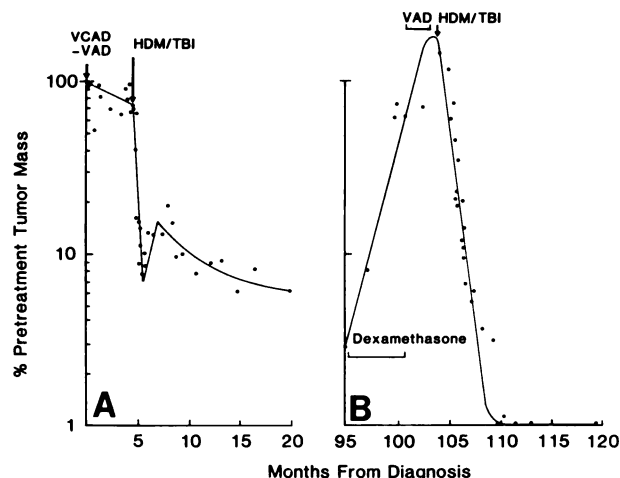


Fig 1. Tumor mass reduction in refractory myeloma following high-dose melphalan (HDM)/TBI and autologous bone marrow support. (A) Primary refractory disease. A 46-year-old patient failed to respond to initial VAD plus cyclophosphamide but responded to HDM/TBI despite marked plasmacytosis of 30% in the marrow autograft. (B) Third relapse. This 50-year-old patient had responded previously but achieved even greater cytoreduction after HDM/TBI.

autografts contained 27% and 30% plasma cells. One of these patients (JH) died from pneumonia 2½ months after treatment with poor marrow engraftment. A second patient (BL) with >90% cytoreduction died after 3 months (with early signs of relapse) from uncontrolled osteomyelitis, which had developed following surgical reduction of a femoral fracture. Three patients remain in remission without further therapy at 2, 11, and 21 months after chemoradiotherapy; the other two patients have developed signs of early relapse at 6 and 15 months, but currently do not require cytotoxic treatment. Five patients were discharged from the hospital within 2 months and have resumed normal activities.

Despite extensive prior therapy (including HDM alone in a 63-year-old patient, ES) and varying degree of marrow plasmacytosis, the hematologic recovery was prompt in six of seven patients treated. The median recovery time of granulocytes to 500/ μ L was 25 days (range, 19 to 62 days) and of platelets to 50,000/ μ L was 41 days (range, 20 to 99+ days). Within 3 months after treatment, granulocytes exceeded 1500/ μ L and platelets 100,000/ μ L in five of the seven patients; these five patients eventually achieved normal

hemograms with average values for hemoglobin of 12.9g%, for granulocytes of 3,200/ μ L and for platelets of 250,000/ μ L. In addition, their marrow biopsies and aspirates showed normal cellularity and differential counts, respectively, without detectable monoclonal plasmacytosis on flow cytometry. One patient (BL) remained thrombocytopenic at a level of 50,000/ μ L until his death, 3 months after therapy, from osteomyelitis and sepsis after surgical reduction of femoral fracture. A second patient (JH) with 27% plasma cells in the autograft had only partial engraftment with persistent neutropenia of <750/ μ L and severe thrombocytopenia <10,000/ μ L.

Four patients had fever without documented infection during the seven to ten days of agranulocytosis, prompting empiric administration of intravenous antibiotics. Three patients required ventilator support for pneumonia, two short-term (BL and ES), whereas the third patient (JH) with slow marrow engraftment died from interstitial pneumonitis, with marked pulmonary fibrosis and no evidence of myeloma at autopsy.

DISCUSSION

While the prognosis of individual patients is often uncertain, none of our patients was expected to live more than 8 months without disease control. Only 15 of 37 comparable patients had responded previously to HDM alone at doses ranging from 50 to 140 mg/M² (90 and 100 mg/M², 17 patients) with a relapse-free and overall survival of only 3 and 5 months, respectively (Table 2).⁵ In contrast, and stressing the cytoreductive potency of added TBI in plasma cell myeloma,⁶ HDM/TBI provided more frequent and marked cytoreduction with a median remission time of 15 months and five of seven patients surviving from 2 to 21 months (median, 9+ months). When administered without BMT, HDM was associated with a high early mortality rate of about 25%, which was reduced markedly by BMT support despite higher doses of cytotoxic therapy (Table 2). The poor marrow engraftment in one of our patients may be attributable to a high degree of plasmacytosis (27%), although a similar patient had prompt hematologic recovery and remains in remission with normal marrow and peripheral hemogram more than 1½ years after therapy.

Because of the reduced tolerance to graft-v-host disease with allogeneic BMT in older patients, marrow-ablative therapy has not been explored systematically in multiple myeloma. Cyclophosphamide/TBI and modifications with

Table 2. High-Dose Melphalan for Refractory Myeloma

HDM (mg/M ²)	TBI (850cGy)	BMT	N	Median Age (yr)	R	(CR)	ED	Median Survival (mo)
<90	—	—	13	62	3	(0)	4	4
90-100	—	—	17	46	8	(1)	4	4
140	—	Auto	7	63	4	(0)	1	6
140	+	Auto	7	50	6	(0)	1	Not reached
140	+	Allo	2	40	2	(2)	0	6, 14*

Abbreviations: HDM, high-dose melphalan; TBI, total body irradiation; BMT, bone marrow transplantation; N, no. of patients; R, patients with >75% tumor reduction including three achieving complete disappearance of M protein by immunofixation (CR); ED, early death; Auto, autologous; Allo, allogeneic bone marrow transplantation.

*Individual survival of two patients.

syngeneic or allogeneic BMT have been effective in about a dozen patients, many of whom still had drug-responsive myeloma.¹³⁻¹⁹ However, myeloma protein disappearance did not occur in any patient with progressive or unresponsive disease and was also not observed in the current study with TBI/HDM when supported by autologous BMT. The induction of complete remission in two additional patients with advanced and VAD-refractory myeloma receiving allogeneic BMT with TBI/HDM may suggest superior activity of HDM to high dose cyclophosphamide, as was evident from previous trials where only two of 15 patients responded briefly to high dose cyclophosphamide alone in contrast to a 48% response rate with HDM.^{5,20} Thus, HDM appears to be at least as effective as high dose cyclophosphamide when combined with TBI. One allogeneic BMT recipient died 6 months after therapy from pneumocystis carinii pneumonia with signs of early disease recurrence; and the second patient committed suicide still in complete remission 14 months after treatment (Table 2).

Because of their older age and the risk of fatal graft-v-host disease, most myeloma patients are candidates for autologous rather than allogeneic BMT. The tolerance of TBI/

HDM by a 63-year-old patient with primary unresponsive myeloma despite VAD and even HDM alone, with hematologic reconstitution from bone marrow harvested 1 year after HDM, suggests that this program can also be considered for patients initially requiring HDM alone because of marked marrow plasmacytosis. While the reinfusion of tumor cells is potentially detrimental to the use of autologous BMT, such an application seemed justified by the slower cell cycle kinetics of myeloma cells, in comparison with regenerating normal bone marrow.²¹ In addition, the terminally differentiated B cells that comprise this tumor have an unusually low in vitro, and perhaps in vivo, cloning efficiency.²² Thus, a selective growth advantage of normal hemopoietic cells over reinfused malignant plasma cells might be expected. While there is considerable interest in removing tumor cells from autologous marrow grafts by immunologic and/or cytotoxic means, such purging procedures must be specific for tumor cells so that hemopoietic engraftment is not compromised. The effectiveness of TBI/HDM, when supported by autologous BMT, provides a new approach to the therapy of patients with refractory myeloma and justifies further study in selected responding patients at high risk for relapse.

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