

Thiotepa, Busulfan, and Cyclophosphamide: A New Preparative Regimen for Autologous Marrow or Blood Stem Cell Transplantation in High-Risk Multiple Myeloma

By Meletios A. Dimopoulos, Raymond Alexanian, Donna Przepiorka, Jeane Hester, Borje Andersson, Sergio Giralt, Rakesh Mehra, Koen van Besien, Kay B. Delasalle, Christopher Reading, Albert B. Deisseroth, and Richard E. Champlin

Forty patients with multiple myeloma received thiotepa (750 mg/m²), busulfan (10 mg/kg), and cyclophosphamide (120 mg/kg) (TBC) followed by autologous bone marrow or blood stem cell support. Granulocyte-Colony stimulating factor (G-CSF) was administered to accelerate hematopoietic recovery. Sixty-five percent of all patients responded to this treatment. Eighty-eight percent of patients transplanted in partial remission had a further reduction of the myeloma and 53% achieved a complete remission. Forty-eight percent of patients with refractory myeloma responded. All responding patients transplanted during par-

tial remission or with primary refractory myeloma remain free of progression for a period of 4 to 24 months post-transplant, but the remission duration of patients treated in refractory relapse was short (4 months). Five of 24 patients transplanted with marrow and none of 16 receiving blood stem cells died of treatment-related complications. Use of blood stem cells resulted in more rapid granulocyte and platelet recovery. We conclude that TBC is an effective, relatively well tolerated, preparative regimen for patients with multiple myeloma.

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DURING THE LAST decade, dose intensive therapy with autologous bone marrow or blood stem cell transplantation has emerged as a useful treatment for selected patients with multiple myeloma.¹⁻⁴ High-dose melphalan combined with total body irradiation (TBI) has been the most frequently used conditioning regimen. A marked cytoreduction has been achieved in the majority of patients and the outcome of those treated in early phases of their disease appears better than that of patients treated during refractory relapse.⁵ Although radiotherapy is effective for multiple myeloma, higher doses are required for local control than can be administered as TBI. In addition, many patients are ineligible for TBI because of previous radiotherapy to the spine.

Alkylating agents are active drugs for treatment of multiple myeloma. There has been considerable interest in combinations of alkylating agents with nonoverlapping extramedullary toxicities as preparative regimens for marrow transplantation.^{6,7} The busulfan-cyclophosphamide combination has shown activity in patients with myeloma undergoing allogeneic bone marrow transplant,^{8,9} but this regimen has substantial toxicity, particularly hepatic veno-occlusive disease in heavily pretreated patients.^{10,11} Thiotepa is an active agent against multiple myeloma;⁵ it is limited by cutaneous and mucosal toxicity and at very high doses can have central nervous system effects.¹² To determine if addition of thiotepa to a reduced dose of busulfan and cyclophosphamide would be a tolerable and effective preparative regimen, we conducted a phase II study of a

combination of these three alkylating agents, with autologous bone marrow or stem cell transplantation.

PATIENTS AND METHODS

Eligibility criteria. Between May 1991 and December 1992, 40 consecutive patients with multiple myeloma were treated. The study was reviewed and approved by the University of Texas M.D. Anderson Institutional Review Board and all patients provided written informed consent. Eligibility criteria included patient age less than 65 years, performance status ≤ 2 on the Zubrod scale, and adequate organ function (creatinine clearance ≥ 50 mL/min, diffusion lung capacity $\geq 50\%$ of predicted, and left ventricular ejection fraction $\geq 50\%$). Patients were treated during resistant relapse, primary resistance, or, in high-risk patients, during remission either after primary treatment or after salvage chemotherapy treatment. Autologous bone marrow was used when marrow plasma cells were less than 30%. The harvested marrow was required to have at least 1.5×10^8 /kg normal nucleated marrow cells and 1×10^4 colony forming unit-granulocyte macrophage (CFU-Gm)/kg. When less than 5% bone marrow plasma cells were present, the marrow was depleted of B-lymphoid precursors using anti-CD19 monoclonal antibody and immunomagnetic beads.¹³ Patients with greater than 30% bone marrow plasmacytosis, prior radiotherapy to the pelvis or lumbosacral spine, or inadequate colony forming units on marrow harvest were eligible for collection of blood progenitors by leukapheresis.

Patients. Patient characteristics are shown in Table 1. Median age of all patients was 49 years (range, 34 to 64 years). Twenty-eight were male and 12 were female. Patients were staged as high, intermediate, and low tumor mass myeloma according to standard criteria.¹⁴ Thirteen newly diagnosed patients who presented with either high or intermediate tumor mass were transplanted in first partial remission. Four patients who were resistant to melphalan and prednisone responded to a subsequent vincristine, doxorubicin, dexamethasone (VAD)-rescue treatment and were transplanted in second partial remission.¹⁵ No patient was in complete remission before myeloablative treatment. Fifteen patients, classified as primary refractory, had never responded to standard therapy and VAD; 10 of them were also resistant to a high-dose cyclophosphamide-etoposide salvage regimen.¹⁶ Eight patients were transplanted during relapse despite a salvage treatment (refractory relapse). Nine of the 40 patients had previously received radiotherapy to the spine at doses precluding use of a TBI-containing ablative regimen.

Autologous marrow. Eleven patients transplanted in first or second partial remission with less than 5% marrow plasma cells received autologous bone marrow depleted of B-lymphoid precursors

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

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Address reprint requests to Richard E. Champlin, MD, Department of Hematology, Section of Bone Marrow Transplantation, 1515 Holcombe Blvd, Box 65, Houston, TX 77030.

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Table 1. Patient Characteristics at Transplantation

	First Partial Remission	Second Partial Remission	Primary Refractory	Refractory Relapse
No.	13	4	15	8
Median age (range)	51 (34-64)	44 (37-49)	46 (37-60)	52 (38-59)
Tumor mass				
High or intermediate	0	0	9	4
β_2 -microglobulin >3 mg/dL	3	0	8	6
Median months from initial treatment (range)	5 (2-12)	20 (13-28)	9 (3-25)	21 (17-52)
Source of stem cells				
Unpurged marrow	0	0	5	8
CD19-purged marrow	9	2	0	0
Blood stem cells	4	2	10	0

using anti-CD19 monoclonal antibody and immunomagnetic beads.¹³ Percoll separated mononuclear cells were incubated with IgG anti-CD19 monoclonal antibody at 4°C for 30 minutes at 1×10^8 cells/mL. Sheep antimouse IgG1 conjugated magnetic beads (Dyna-beads M-450) were added at a concentration of 2 beads per cell and incubated for 30 minutes at 4°C on a tilting device. The cell suspension was passed through the separation device at a flow rate of 20 mL/min at 4°C into a collection bag and then cryopreserved in 10% DMSO using standard techniques. The percentage of CD19⁺ cells in the percoll separated fractions ranged from 0.2% to 14.3% (median, 2.9%) before immunomagnetic purging. After this procedure, 6 of 11 patients did not have demonstrable CD19⁺ by immunofluorescence while the remaining patients had between 0.2% and 0.8% residual CD19 cells. Immunomagnetic purging resulted in a median recovery of 80.7% CD34⁺ cells (range, 36.9% to 100%) after the procedure.

Five patients with primary refractory myeloma were transplanted with unmanipulated autologous bone marrow, which contained less than 30% plasma cells, whereas 10 patients with more heavily infiltrated marrow received autologous blood stem cells. All patients with myeloma in refractory relapse received unmanipulated autologous bone marrow that was harvested during a prior remission when bone marrow plasma cells were less than 5%.

Blood stem cell collection. Six patients in first or second partial remission who had previously received radiotherapy to the pelvis or lumbosacral spine and 10 patients with marrow plasmacytosis greater than 30% underwent blood stem cell collection. All patients were hospitalized. A double lumen quinton catheter was inserted into a subclavian vein and a combination of cyclophosphamide 3.0 g/m² intravenously (IV) and etoposide 900 mg/m² IV was administered over 5 days as previously described.¹⁶ On day 6, GM-CSF was started at a dose of 10 µg/kg subcutaneously daily.

Apheresis of blood mononuclear cells was performed with a Cobe Spectra blood cell separator and commenced during hematopoietic recovery when the absolute mononuclear cell (mnc) count was greater than 400/µL. Stem cell collection was performed daily to obtain at least 4×10^8 mnc/kg body weight. Five patients required platelet transfusions to facilitate stem cell collection.

Conditioning regimen and supportive care. The ablative regimen consisted of thiotepa 250 mg/m² in 250 mL normal saline (NS) IV over 4 hours on days -9, -8, and -7; busulfan 1.0 mg/kg orally (PO) every 6 hours for 10 doses on days -6, -5, and -4; cyclophosphamide 60 mg/kg in 200 mL dextrose 5% in water (DSW) IV over 1 hour through a central venous catheter on days -3 and -2. Mesna 250 mg/m² was administered 30 minutes before and every 4 hours for six doses after each cyclophosphamide infusion. Autologous marrow or blood stem cells were reinfused on day 0 through a central venous catheter preceded by methylprednisolone

100 mg IV and benadryl 50 mg IV. On day +1, G-CSF was started at a dose of 10 µg/kg/d, which was continued until granulocyte count exceeded 4,000/µL for 3 consecutive days. The doses of thiotepa, busulfan, and cyclophosphamide (TBC) were those defined in a phase I study in patients with advanced hematologic malignancies.¹⁷

All patients were treated in a private room. Antibiotic prophylaxis included daily oral norfloxacin 800 mg and IV vancomycin 1 g/d; in addition, acyclovir 15 mg/kg and fluconazole 400 mg were administered daily IV. Patients received IV Ig at a dose of 500 mg/kg every 2 weeks starting on day -8.

Toxicity grading. All cases of nonhematologic organ dysfunction were considered regimen related toxicities (RRT) unless they could be clearly explained by another cause (eg, renal failure due to septic shock, respiratory failure due to documented pneumonia). The grading scale described by Bearman et al was used.¹⁸ Grade 0 represented no toxicity; grade 1 toxicity was fully reversible without specific intervention; grade 2 toxicity was not life-threatening, but its reversal required specific measures; grade 3 toxicity was life-threatening but reversible; and grade 4 toxicity was fatal.

Response. Serial measurements of blood counts, chemistries, and electrophoretic studies were conducted. Complete remission (CR) was defined as disappearance of serum monoclonal protein on immunofixation and no evidence of monoclonal plasma cells in the bone marrow for at least 2 months. Partial remission (PR) required $\geq 75\%$ reduction of serum myeloma protein synthesis with disappearance of Bence Jones proteinuria and reduction of bone marrow plasmacytosis to less than 5% for at least 2 months.¹⁹ Patients who died of transplant-related complications (toxic deaths) were considered treatment failures.

Maintenance therapy. Alpha-interferon at a dose of 1×10^6 U subcutaneously three times a week was started when the granulocyte count recovered to greater than 2,500/µL and platelets $\geq 50,000/\mu\text{L}$. The dose of interferon was increased as tolerated to 2×10^6 U/m² three times a week. In addition, dexamethasone 20 mg/m² daily was administered PO for 4 days each month. This maintenance program was continued until there was evidence of disease progression.

RESULTS

Hematologic recovery. All patients experienced profound pancytopenia. Hematologic recovery is summarized in Table 2. G-CSF was well tolerated and its administration was not discontinued in any patient. Median time to granulocyte and platelet recovery was similar in patients transplanted with unmanipulated or CD19-purged marrow. One patient transplanted in second remission with CD19-purged

Table 2. Hematologic Recovery Posttransplant

Stem Cell Source	No.	Median Days (range)		
		Granulocytes >500/ μ L	Platelets	
			>25,000/ μ L	>50,000/ μ L
Unpurged marrow	13	15 (10-29)	35 (11-49)	41 (17-56)
CD19-purged marrow	11	13 (10-36)	27 (16-39)	32 (16-69)
Blood stem cells	16	9 (7-14)	12 (8-58)	15 (9-59)

marrow did not show signs of granulocyte engraftment and bone marrow biopsy showed aplasia on day 21 posttransplant; this patient subsequently recovered when her unpurged marrow was infused. The time to recovery of granulocytes greater than 500/ μ L and platelets greater than 25,000/ μ L was compared among patients transplanted with bone marrow (purged or unmanipulated) with that of patients receiving stem cells (Table 2). Recovery of granulocytes and platelets was significantly more rapid with blood stem cell transplantation ($P = .0001$).

Toxicity. Thirty-five of the 40 patients developed at least grade 1 toxicity (Table 3). The most frequent toxicities were stomatitis and diarrhea, but none developed higher than grade 3 toxicity of the gastrointestinal tract. Four patients (10%) developed grade 3 or 4 RRT, which was fatal in two patients. Eight patients developed thiotepea skin toxicity, which was characterized by pruritus and dermatitis predominantly involving the axillary folds. The skin toxicity was associated with exfoliation in three patients. Pigmentation and tender swelling of the palmar and plantar surfaces occurred in two patients. Cutaneous toxicity was reversible in all patients.

All but three patients developed neutropenic fever. Blood cultures showed gram-positive organisms in seven patients and gram-negative organisms in five; three patients developed documented sinopulmonary aspergillosis. Three patients developed cytomegalovirus (CMV) infection including 1 patient with fatal CMV pneumonia.

Five patients (13%) experienced a treatment-related death. All had been transplanted with autologous marrow. Their median age was 52 years (range, 41 to 59 years). Two had resistant relapse myeloma, two had primary refractory disease, and 1 patient was transplanted in first remission. Two patients died from pneumonia developing during the

aplastic phase; 1 patient died of hepatic venoocclusive disease, and another patient of diffuse alveolar hemorrhage. The fifth patient expired from CMV pneumonia on day 67 posttransplant. None of the patients transplanted with blood stem cells expired.

Response and survival. Among 13 patients transplanted in first PR, 11 had further reduction of the myeloma protein and seven patients achieved a CR (Table 4). All four patients who were transplanted during a second PR showed marked reduction of the myeloma protein with a CR in two patients. Except for one therapy-related death, all patients transplanted in first or second PR remain free of progression from 4 to 20 months posttransplant (Fig 1).

Seven of 15 patients with primary refractory myeloma responded; one achieved CR and 6 a PR. Six failed to respond and two died of transplant-related complications. The median time to achieve remission was 0.9 month (range, 0.1 to 5.0 months) posttransplant. Ten primary refractory patients were not only resistant to standard alkylating agents and VAD, but also failed to respond to cyclophosphamide (3 g/m²) and etoposide (900 mg/m²). Five such patients responded to the TBC regimen. All responding patients remain free of progression (Fig 1).

Four of eight patients with refractory relapse myeloma achieved a PR. Two failed to respond and two died of treatment-related complications. Responses occurred after a median of 0.3 month (range, 0.1 to 0.7). The remission duration in this category was short (median, 4.1 months) and the median survival time after transplant was only 4 months.

Alpha interferon was started at a median day 41 (range, 13 to 76 days) posttransplant in responding patients and was well tolerated with the exception of three patients in whom reversible leukopenia required temporary discontinuation of this therapy. The interferon dose was escalated to 2×10^6 U/m² three times a week in all patients.

DISCUSSION

The combination of thiotepea, busulfan, and cyclophosphamide was designed with a goal to optimize dose intensity by combining three active alkylating agents with nonoverlapping toxicity for treatment of high-risk patients with multiple myeloma. In addition, an opportunity was developed for future studies of repeat transplant-supported therapies in selected patients. The TBC regimen allowed us to treat nine patients who had previously received radiotherapy to the spine in doses that precluded TBI.

Table 3. Regimen-Related Toxicity

	Grade				
	0	1	2	3	4
Mucositis	8	21	11	0	0
Gastrointestinal	24	14	2	0	0
Liver	28	7	1	1	1
Cardiac	37	1	2	0	0
CNS	37	0	0	0	0
Renal	37	1	0	0	0
Bladder	37	1	1	1	0
Pulmonary	36	1	1	0	1

Table 4. Clinical Outcome After Transplant

	No.	Early Death	Myeloma Protein >75% Reduction (CR)	No Response
First partial remission	13	1	11 (7)	1
Second partial remission	4	0	4 (2)	0
Primary refractory	15	2	7 (1)	6
Refractory relapse	8	2	4 (0)	2
Total	40	5	26 (10)	9

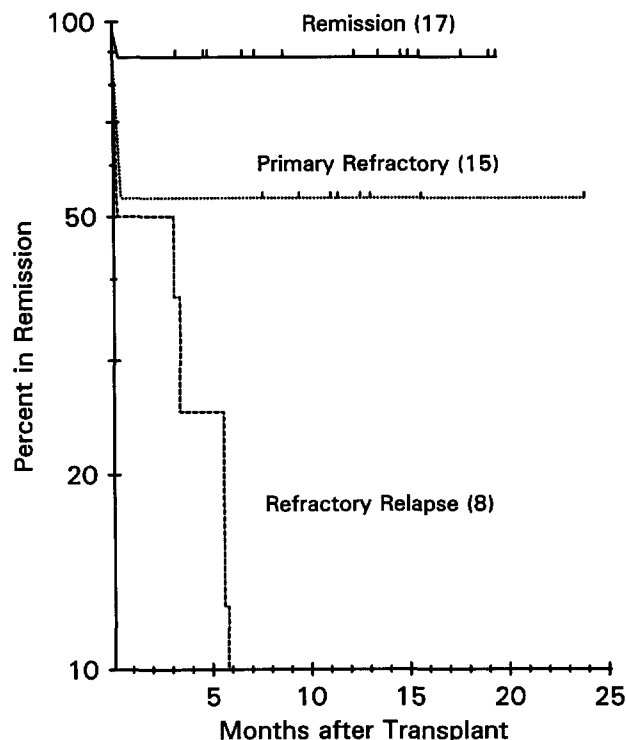


Fig. 1. Progression-free survival for different groups of patients with multiple myeloma; remission curve includes patients in first and second remission. Failure includes no response, relapse, or death from any cause. Numbers in parentheses refer to patients in each category.

Each of the drugs used in this combination has proven activity against myeloma and a different spectrum of extramedullary toxicities. The combination of busulfan and cyclophosphamide with allogeneic marrow transplantation is widely used for patients with leukemia,²⁰ as well as in some patients with multiple myeloma.^{8,9} High-dose busulfan with autologous bone marrow rescue has been recently reported to have activity against resistant myeloma.²¹ To decrease the relatively high incidence of regimen-related toxicity, we reduced the dose of busulfan and introduced thiotepa, which when administered at high doses, is active against myeloma.¹⁵ Furthermore, there is *in vitro* and *in vivo* evidence of synergism between cyclophosphamide and thiotepa.²²

The TBC combination was relatively well tolerated. Reversible skin toxicity, presumably due to thiotepa, occurred in eight patients. Three patients developed higher than grade 2 liver toxicity. No patient developed regimen-related central nervous system side effects. Thirteen percent of patients died as a complication of the treatment, a frequency similar to that observed with melphalan/TBI or other non-TBI-containing regimens.⁴⁻⁶

This trialkylator combination induced a marked cytoreduction of the myeloma in approximately two-thirds of our patients. Using strict criteria, which include negative serum immunofixation, 53% of patients transplanted during first or second PR achieved a CR and myeloma has not yet re-

lapsed in any patient. The TBC regimen induced PR or CR in 50% of patients resistant not only to standard treatments, but also to a high-dose cyclophosphamide-etoposide salvage therapy.¹⁶ The efficacy of myeloablative therapy in patients with primary refractory myeloma, especially when administered during the first year of treatment, has been previously reported.⁵ While one-half of patients transplanted during a refractory relapse phase of myeloma responded, remission duration and subsequent survival were short. This is similar to the experience with melphalan and TBI in this category of patients; such patients have not had meaningful benefit from high-dose therapies and alternative approaches are needed.⁵

The optimal source of autologous stem cell for transplantation in patients with multiple myeloma has not been clearly defined and both marrow and blood stem cells were used in a recent study.²³ Peripheral blood progenitors collected by multiple leukapheresis were the only source of cells for 16 patients with heavily infiltrated bone marrow or with prior radiotherapy to the pelvis or lumbosacral spine. Recovery of normal hematopoiesis occurred earlier than with bone marrow transplantation, and none died from treatment complications, suggesting that blood stem cells may be preferable for the support of ablative therapy for myeloma patients, assuming remission duration is not adversely affected.

Eleven patients were transplanted in partial remission using autologous marrow depleted of B-lineage cells using an anti-CD19 monoclonal antibody and immunomagnetic separation. All but one patient engrafted and the timing of hematopoietic reconstitution was similar to that of patients receiving unmanipulated marrow. Sixty-four percent of such patients achieved CR. A similar study reported recently by Anderson et al²⁴ also demonstrated the feasibility of this approach. Controlled trials are necessary to define the role of autologous marrow purging in this disease. Whether purging of blood stem cells is feasible or necessary also remains to be determined.

Interferon- α and dexamethasone are both active agents against myeloma especially when administered during remission or to patients with low tumor mass disease.^{25,26} Although high-dose therapy with autologous transplantation is effective to produce CR, this approach has not been curative. Posttransplant therapy with these agents was included to suppress residual myeloma likely to be present after high-dose therapy. The impact of maintenance therapy after autologous transplantation can only be assessed in the context of a controlled trial. A preliminary analysis of a randomized trial in myeloma reported that interferon prolonged the progression-free survival when administered after autologous bone marrow transplantation.²⁷

In conclusion, this study indicates that this triple alkylator combination regimen is effective to produce extended remissions in selected patients with multiple myeloma. Controlled studies involving larger numbers of patients with extended follow-up are required to define its role and the optimal timing of the procedure. A high degree of cytoreduction occurred in patients treated during PR or with primary refractory myeloma. Patients with myeloma in refrac-

tory relapse had only transient responses and do not appear to benefit from currently available ablative therapies; alternative approaches should be studied in these patients.

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