Monoclonal Antibody-Purged Bone Marrow Transplantation Therapy for Multiple Myeloma

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Forty patients with plasma cell dyscrasias underwent high-dose chemoradiotherapy and either anti-B-cell monoclonal antibody (MoAb)-treated autologous, anti-T-cell MoAb-treated HLA-matched sibling allogeneic or syngeneic bone marrow transplantation (BMT). The majority of patients had advanced Durie-Salmon stage myeloma at diagnosis, all were pretreated with chemotherapy, and 17 had received prior radiotherapy. At the time of BMT, all patients demonstrated good performance status with Karforsky score of 80% or greater and had less than 10% marrow tumor cells; 34 patients had residual monoclonal marrow plasma cells and 38 patients had paraprotein. Following high-dose chemoradiotherapy, there were 18 complete responses (CR), 18 partial responses, one non-respond and three toxic deaths. Granulocytes greater than 500/μL and untransfused platelets greater than 20,000/μL were noted at a median of 23 (range, 12 to 46) and 25 (range, 10 to 175) days posttransplant (PT), respectively. In the 14 patients who received allogeneic or syngeneic grafts, granulocytes greater than 500/μL and untransfused platelets greater than 20,000/μL were noted at a median of 19 (range, 12 to 24) and 16 (range, 5 to 32) days PT, respectively. With 24 months median follow-up for survival after autologous BMT, 16 of 26 patients are alive free from progression at 2+ to 55+ months PT; of these, 5 patients remain in CR at 8+ to 55+ months PT. With 24 months median follow-up for survival after allogeneic and syngeneic BMT, 8 of 14 patients are alive free from progression at 8+ to 34+ months PT; of these, 5 patients remain in CR at 8+ to 34+ months PT. This therapy has achieved high response rates and prolonged progression-free survival in some patients and proven to have acceptable toxicity. However, relapses post-BMT, coupled with slow engraftment post-BMT in heavily pretreated patients, suggest that such treatment strategies should be used earlier in the disease course. To define the role of BMT in the treatment of myeloma, its efficacy should be compared with that of conventional chemotherapy in a randomized trial.

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Collection, processing, and infusion of marrow. Bone marrow mononuclear cells (BMMCs) were obtained from the iliac crests, collected in RPMI-1640 medium with preservative-free heparin, filtered through stainless-steel mesh, and then washed and concentrated using a COBE 2991 cell washer (COBE Laboratories, Lakewood, CO). Ex vivo treatment of autologous BM was based on previously reported methods developed at the Dana-Farber Cancer Institute that reproducibly deplete two to three logs of antigen (Ag) positive-cells without depleting hematopoietic stem cells.43 Specifically, anti-PCA-1 MoAb and complement in vitro can lyse two to three logs of the RPMI 8226 myeloma cell line. Mononuclear cells were isolated on Ficoll-Hypaque gradients and resuspended in RPMI-1640 at a concentration of 2 × 10^6 cells/mL. These cells were subjected to three treatments, each consisting of a 30-minute incubation with MoAb at 20°C followed by incubation for 30 minutes at 37°C with rabbit complement (Pel Freeze, Brown Deer, WI). Marrow cells were treated with MoAbs directed at three Ags, including CALLA (CD10), which detects the common acute lymphoblastic leukemia Ag;43 B1 (CD20), a pan-B cell Ag; and PCA-1, which detects a plasma-cell-associated Ag.44 This MoAb cocktail was used to target cells in the malignant clone from the pre-B-cell to the plasma stage.44 Before in vitro marrow treatment, phenotypic analysis demonstrated less than 10% of cells bearing the CALLA, B1, or PCA-1 Ags; after treatment, repeat analysis showed absence of cells bearing these Ags. Cells were then cryopreserved in medium containing 10% dimethyl sulfoxide and 90% autologous serum at -196°C in the vapor phase of liquid nitrogen. Before infusion, the cryopreserved marrow cells were rapidly thawed and diluted in medium containing 25 IU DNase/mL to minimize clumping. The median number of reinfused marrow cells was 2.1 × 10^9 (range, 1.4 to 5.2 × 10^9), or a median of 3.1 × 10^9/kg (range, 1.8 to 7.8 × 10^9/kg), with 85% to 95% viability as measured by Trypan blue exclusion.

For autologous BM, BM was harvested from histocompatible sibling donors under general anesthesia using standard techniques. Marrow was anticoagulated with preservative-free heparin in RPMI 1640. After BM harvest, marrow cells were washed free of the anticoagulant and plasma proteins and concentrated into a 50 to 100 mL buffy-coat fraction using a COBE 2991 blood-cell processor. Bone marrow mononuclear cells were isolated from the buffy-coat fraction on discontinuous gradients of Ficoll-Hypaque. Mononuclear cells were placed at a cell concentration of 2 × 10^7/mL and were incubated with anti-T12 (CD6) MoAb (IgM isotype) for 15 minutes at 20°C followed by the addition of rabbit complement at a ratio of 1:8 or 1:10 final dilution for further incubation at 37°C for 45 minutes. Our method for in vitro treatment of marrow with anti-T12 MoAb to abrogate graft-versus-host disease (GVHD) was described previously.46 Incubation with anti-T12 and complement was repeated twice. After completion of treatment, marrow cells were combined and washed five times to remove both MoAb and complement, and were then resuspended in 50 mL media that contained 10% human AB serum. After T12 treatment, patients received a median of 6.3 × 10^9 (range, 2.5 to 10 × 10^9) or a median of 7.4 × 10^7 (range, 2.7 to 13 × 10^7) cells/kg.

The single patient who underwent syngeneic BMT received non-purged marrow with 82.5 × 10^9 total cells, or 101.2 × 10^9 cells/kg.

Supportive care. Patients were treated in reverse-isolation rooms until they were discharged. Discharge was permitted if the absolute granulocyte count was stable at greater than 500/μL, and no fever had occurred in the absence of antibiotics for 24 to 48 hours. Trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis was begun in all patients when chemotherapy was initiated, but was discontinued if intravenous broad-spectrum antibiotics were required. Patients received prophylactic acyclovir (5 mg/kg or

Materials and methods

Selection of patients and treatment protocol. Patients were eligible for autologous BMT if they were less than 60 years of age; patients less than 55 years of age who had histocompatible sibling donors underwent autologous BMT. All patients had multiple myeloma, as well as reactivity of tumor cells with anti-plasma cell associated-1 (PCA-1) MoAb. All original laboratory parameters were reviewed to establish a proper Durie-Salmon stage at diagnosis. Patients must have achieved a minimal tumor burden, defined as less than 10% BM tumor cells (regardless of serum paraprotein) before BMT. Pretransplant therapy was administered to achieve maximum cytoreduction either at Dana-Farber Cancer Institute (DFCI) or, under its supervision, administered at local institutions. Sites of bony disease received additional radiation therapy before BMT. Additional criteria for entry included the absence of comorbid disease of the heart, kidney, lung, and liver, and a Karnovsky score above 80%. Patients whose prior radiotherapy obviated the ability to deliver full-dose total body irradiation (TBI) received ablative therapy with chemotherapy only. In patients less than 55 years of age who had HLA identical mixed lymphocyte culture (MLC) nonreactive sibling donors, allogeneic grafting was performed in preference to autologous BMT; autologous grafting was done for patients less than 60 years of age, including those less than 55 years of age who did not have histocompatible sibling donors. Written informed consent was obtained from all patients for treatment protocols approved by the Human Protection Committee at DFCI.

Preparative therapy for patients undergoing autologous BMT included melphalan 70 mg/m² of body weight, infused on each of 2 consecutive days before 1,200 cGy TBI in 20 patients; and cyclophosphamide 60 mg/kg of body weight, infused on each of 2 consecutive days before TBI (1,200 cGy in one patient and 1,400 cGy in five patients). The initial 11 patients who received melphalan 70 mg/m² on 2 consecutive days followed by 1,200 cGy TBI were evaluated for toxicity in a phase I study.35 Ablative therapy included cyclophosphamide 60 mg/kg of body weight, infused on each of 2 consecutive days before 1,400 cGy TBI in 11 recipients of allografts and the sole recipient of syngeneic marrow; and busulfan 1 mg/kg of body weight orally every 6 hours for 16 doses over 4 consecutive days before cyclophosphamide 60 mg/kg of body weight infused on 2 consecutive days in two allotransplant patients who had received prior radiotherapy which precluded TBI. Within 18 hours of the completion of radiotherapy, either (1) cryopreserved autologous BM that had been previously treated in vitro with anti-CD10, anti-CD20, and anti-PCA-1 MoAbs and rabbit complement to deplete tumor cells was thawed rapidly and reinfused; or (2) allogeneic marrow that had been treated with anti-CD6 MoAb and rabbit complement to deplete T cells was reinfused fresh. Marrows were administered through a central venous catheter.
400 mg orally every 8 hours) for Herpes simplex infections. Prophylaxis with trimethoprim-sulfamethoxazole or pentamidine inhaler was instituted at the time of discharge and continued for 12 months to prevent *Pneumocystis carinii* pneumonia. Patients were also treated with acyclovir to prevent Herpes zoster infection during the first 12 months posttransplant. Cytomegalovirus-negative blood products were used in all patients, regardless of prior exposure to the virus. Blood products were irradiated (2,500 cGy) to prevent transfusion-related GVHD.

Clinical evaluation. Before treatment, all patients were evaluated as follows: physical examination, blood chemistry profile, complete blood count, serum and urinary protein immunoelectrophoresis and immunofixation, human immunodeficiency virus serology, bone survey, bilateral BM biopsies and phenotypic analysis of BMMCs, pulmonary function tests, and ventriculogram. Criteria for CR included, for at least 3 months, both (1) the absence of serum paraprotein and Bence Jones proteinuria by immunoelectrophoresis and immunofixation; and (2) fewer than 5% polyclonal plasma cells, as demonstrated by immunoperoxidase staining of BM biopsy specimens for Ig heavy and light chains. A 50% decrease in measurable protein sustained for at least 1 month constituted a partial response. Follow-up evaluations included serum protein studies monthly and BM aspiration and biopsy at 3-month intervals for the first year PT; protein studies at 3-month intervals and BM aspiration and biopsy at 6-month intervals for the second year PT; and protein studies at 3-month intervals thereafter. Radiographic bone surveys were performed at 12 month intervals.

*α* 2*β* IFN maintenance therapy. For patients treated since 1990, *α* 2*β* IFN therapy, 3 × 10⁶ U subcutaneously 3 times weekly, has been used beginning at 3 months PT and continued for at least 9 months PT in an attempt to prolong the duration of responses achieved. IFN was not used in patients who did not achieve transfusion independence with granulocytes ≥1,500/µL and PLTs ≥100,000/µL by 3 months PT.

Statistical methods. Survival and failure-free survival (FFS) were calculated from date of BMT. Cases were censored for FFS if alive and disease free at analysis. Three patients who underwent autologous BMT died free from progression at 2, 6, and 19 months, and are considered failures for this analysis. This underestimates FFS, but perhaps better reflects the experience of the patients.

**RESULTS**

Patient characteristics. Twenty-five patients with myeloma and 1 patient with recurrent extramedullary plasmacytomas underwent autologous BMT between February 1987 and November 1992 (Table 1). There were 16 men and 10 women with a median age of 47 (35 to 59) years, including 2, 4, 13, and 6 patients with Durie-Salmon stages I A, II A, III A, and IIIB disease, respectively, at time of diagnosis. Serum β₂ microglobulin and BM labeling indices were not routinely performed. Patients received a median of three (two to four) treatment regimens over a period of 23 (8 to 52) months before BMT. Fourteen patients had received radiotherapy before BMT. At the time of autologous BMT, all patients had sensitive disease in that they had achieved minimal disease status, defined as less than 10% BM plasma cells. Three patients had polyclonal plasma cells evident on bilateral bone marrow biopsy; 1 of these also had no serum and/or urine monoclonal protein and was therefore the only patient in complete remission. The remaining patients demonstrated both monoclonal marrow plasma cells and monoclonal paraprotein at the time of autologous BMT.

Thirteen patients with multiple myeloma underwent allogeneic BMT between February 1990 and November 1992 (Table 1). There were 9 men and 4 women with a median age of 43 (37 to 52) years, including 2, 3, 6, and 2 patients with Durie-Salmon stages I A, II A, III A, and IIIB disease, respectively, at the time of diagnosis. Serum β₂ microglobulin and BM-labeling indices were not routinely performed. Patients received a median of two (one to four) treatment regimens over a period of a median of 25 (9 to 48) months before BMT. Three patients had received radiotherapy before BMT. At the time of allogeneic BMT, all patients again had sensitive disease and achieved minimal disease status, defined as less than 10% BM plasma cells. Three patients had polyclonal plasma cells evident on bilateral bone marrow biopsy; 1 of these also had no serum and/or urine monoclonal protein and was therefore the only patient in complete remission. The remaining patients demonstrated both monoclonal marrow plasma cells and monoclonal paraprotein at the time of allogeneic BMT.

*α* 2*β* IFN therapy was not used in patients who did not achieve transfusion independence with granulocytes ≥1,500/µL and PLTs ≥100,000/µL by 3 months PT.

**Statistical methods.** Survival and failure-free survival (FFS) were calculated from date of BMT. Cases were censored for FFS if alive and disease free at analysis. Three patients who underwent autologous BMT died free from progression at 2, 6, and 19 months, and are considered failures for this analysis. This underestimates FFS, but perhaps better reflects the experience of the patients.

<table>
<thead>
<tr>
<th>Source of Stem Cells</th>
<th>No. of Patients</th>
<th>Median Age (yr) (range)</th>
<th>Sex</th>
<th>No. of Patients: Stage at Diagnosis</th>
<th>No. of Patients: Isotype</th>
<th>No. of Patients: ChemoRx Regimens Before Transplant</th>
<th>No. of Patients: RadioRx Before Transplant</th>
<th>Median Interval Diagnosis to Transplant (mo) (range)</th>
<th>No. of Patients With (+) or Without (−) Monoclonal Plasma Cells at Transplant</th>
<th>No. of Patients With (+) or Without (−) Monoclonal Protein at Transplant</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>10 F</td>
<td>4:IA</td>
<td>7:lgA</td>
<td>11:3</td>
<td>12−</td>
<td>−</td>
<td>3−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13:IIA</td>
<td>3:K or λ</td>
<td>8:4</td>
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<td></td>
<td></td>
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<tr>
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<tr>
<td></td>
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<td></td>
<td>F</td>
<td>4 F</td>
<td>3:IIA</td>
<td>2:lgA</td>
<td>7:2</td>
<td>10−</td>
<td>3</td>
<td>1</td>
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<td>2:IIIB</td>
<td></td>
<td>2:4</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Syngeneic marrow</td>
<td>1</td>
<td>44</td>
<td>M</td>
<td>1 M</td>
<td>III</td>
<td>IgG</td>
<td>1:1</td>
<td>−</td>
<td>8</td>
<td>−</td>
</tr>
</tbody>
</table>
at a median of 23 (range, 12 to 46) days PT in 25 patients and untransfused platelets greater than 20,000/µL at a median of 25 (range, 10 to 175) days PT in 24 of the 26 patients (Table 2). A median of 9 U (range, 4 to 30 U) of red blood cells (RBCs) and 56 U (range, 4 to 329 U) of platelets were transfused. Patients were discharged from the hospital at a median of 25 (range, 12 to 52) days PT. A single patient who underwent autologous grafting, all developed fevers (>101°F) while leukopenic, but only 3 patients had positive blood cultures: Staphylococcus epidermidis in 2 patients and α-hemolytic streptococcus in a single patient (Table 2). Eighteen patients developed mucositis. Herpes zoster and venous thrombosis occurred in 4 and 1 patient, respectively. Three patients developed hypothyroidism and a single patient hypoparathyroidism PT.

As noted above, there was 1 acute in-hospital treatment-related death. This death occurred in a 50-year-old woman who presented with plasmacytoma of the proximal left femur necessitating hip replacement, associated with Durie-Salmon stage IIIB multiple myeloma. After the next 2 years she received therapy with four combination chemotherapy regimens (total dose of 90 mg carmustine). After melphalan and TBI-ablative therapy, she received 2.9 × 10^7 cells/kg bone marrow infusion. Fever without source was noted on day 5 PT and leukocytes reappeared as expected by day 10 PT. Her hospital course was complicated by pneumonia (day 11 PT), a diffuse rash thought to be drug-related (day 30 PT), and clinical and radiographic findings consistent with typhilitis (day 50 PT). BM aspirate at day 41 PT was hypocellular, but without evidence of myeloma, and leukocyte count peaked on day 48 PT at 800/µL with 40% granulocytes. Despite aggressive antibiotic and transfusion support, the patient became alloimmunized and refractory even to HLA-matched platelet transfusions and succumbed with a central nervous system hemorrhage on day 67 PT. Postmortem examination showed numerous petechial and ecchymotic lesions of the skin and serosal surfaces of the peritoneum, pleura, and pericardium, as well as hemorrhage of the respiratory, gastrointestinal, and urothelial mucosa. The BM was hypocellular but all cell lines were recovering; immunoperoxidase studies of marrow indicated that the scattered plasma cells were of a polyclonal nature.

Of the 13 patients who underwent allogeneic grafting, 11 developed fever (>101°F) while leukopenic (Table 2). Blood cultures were positive in 3 patients: Staphylococcus

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**Table 2. Hematologic Engraftment and Toxicity After BMT for Myeloma**

<table>
<thead>
<tr>
<th>Source of Stem Cells</th>
<th>No. of Patients</th>
<th>Median Days PT With Granulocytes &gt;500/µL</th>
<th>Median Days PT to Platelets &gt;20,000/µL</th>
<th>Median Units of RBCs Transfused</th>
<th>Median Units of Platelets Transfused</th>
<th>Median Days in Hospital</th>
<th>No. of Patients: Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purged autologous marrow</td>
<td>26</td>
<td>23 (12-46)*</td>
<td>25 (10-175)*</td>
<td>9 (4-30)</td>
<td>56 (4-329)</td>
<td>31 (24-67)</td>
<td>26: Fever</td>
</tr>
<tr>
<td>T-depleted allogeneic marrow</td>
<td>13</td>
<td>19 (12-24)</td>
<td>16 (5-32)</td>
<td>8 (4-23)</td>
<td>45 (17-307)</td>
<td>31 (27-52)</td>
<td>11: Fever</td>
</tr>
<tr>
<td>Syngeneic marrow</td>
<td>1</td>
<td>19</td>
<td>25</td>
<td>6</td>
<td>76</td>
<td>33</td>
<td>1: Fever</td>
</tr>
</tbody>
</table>

Abbreviation: PT, posttransplant.

* One patient did not achieve greater than 500 granulocytes/µL and 2 patients did not achieve untransfused platelets greater than 20,000/µL.
greater than 500/µL and platelets greater than 20,000/µL at
with corticosteroids and cyclosporine for
brother who was both HLA and AB0 compatible. On day
gain, ascites, and liver function test abnormalities in the first
evidence of residual myeloma in marrow.
was refractory to immunosuppressive therapy including cor-
brother's non-T-cell depleted marrow, after preparation
found venous congestion and biliary stasis and ascites was
present. Characteristic signs of GVHD in the gastrointesti-
not was present, nor was there any
other infection was documented, and a trial of granulocyte
achieved pathologically normal marrows with less than
5% plasma cells were polyclonal on immunoperoxidase stain-
were also absent in serum and urine, and monoclonal plasma cells were polyclo-
al on immunoperoxidase staining. On staging marrow
biopsies performed routinely during the first 24 months PT, the presence of less than 5% polyclonal plasma cells was
confirmed in 11 patients (7 complete and 4 partial re-
sponders) at a median of 4 (2 to 8) months PT. In 2 of the 7
complete responders, mononuclear plasma cells have re-
turned at 6 and 7 months PT. Monoclonal proteins disap-
ppeared in the 7 patients with CR at a median of 3 (1 to 4)
months PT; in 2 of the 7 complete responders, monoclonal
protein also returned at 6 and 7 months PT. Of the 7 com-
plete responders to allogeneic BMT, normal levels of IgG,
IgA, and IgM were noted in 5, 6, and 7 patients at 5 (range, 2
to 12), 5 (range, 2 to 14), and 5 (range, 1 to 6) months PT,
respectively. Of the 4 partial responders, normal levels of the uninvolved IgG,
IgA, and IgM were noted in 4, 1, and 1
patient at 5, 2, and 3 (range, 2 to 5) months PT, respectively.
Polyclonal elevation of IgG and monoclonal IgG protein have each been noted in a single patient at 14 and 9 months
PT, respectively.

Therapeutic results. Among the patients who under-
went autografting, there were 11 complete and 14 partial
responders, and 1 toxic death. All responding patients
achieved pathologically normal marrows with less than 5%
marrow plasma cells; in complete responders, monoclonal
proteins were also absent in serum and urine, and monoclonal plasma cells were polyclonal on immunoperoxidase staining. Staging marrow biopsies routinely performed during the first 24 months PT confirmed the presence of less than 5% polyclonal plasma cells in 21 patients (11 complete and 10 partial responders) at a median of 3 (range, 3 to 10) months PT. Monoclonal proteins disappeared in 11 patients with CR at a median of 3 (range, 2 to 19) months PT. Of the 11 complete responders to autologous BMT, normal levels of IgG, IgA, and IgM were noted in 5, 8, and 9 patients at 9 (range, 6 to 13), 5 (range, 1 to 10), and 6 (range, 1 to 10) months PT, respectively. Of the 14 partial responders, nor-
mal levels of IgG, IgA, and IgM were noted in 2, 6, and 12
patients at 1 and 24, 9 (range, 5 to 12), and 4 (range, 1 to 12) months PT, respectively. One patient had free λ light chains in serum and urine before BMT and recurred with IgG λ after BMT. Another patient had IgA λ myeloma before BMT and recurred with IgA λ as well as IgG λ monoclonal proteins.

As of November 1, 1992 with 24 months median follow-
up, 21 of the 26 patients who underwent autografting are alive at 2+ to 68+ months PT, and 16 patients remain alive free from progression at 2+ to 55+ months PT (Fig 1); of
these, five patients remain in CR at 6+ to 55+ months PT. Three patients died free from progression at 2, 6, and 19
months PT. Seven patients relapsed at 3 to 36 months PT; of
these, 5 patients remain alive at 22+ to 68+ months PT, and 2 patients died at 14 and 27 months PT. The median
progression-free survival is 36 months and median overall
survival has not yet been reached.

Among the 14 patients who received either allogeneic or
syngeneic grafts, there were 7 complete responders, 4 partial
responders, 1 non-responder, and 2 toxic deaths. Again, all
responding patients achieved pathologically normal marrows with less than 5% marrow plasma cells; in complete responders, monoclonal proteins were also absent in
serum and urine, and monoclonal plasma cells were polyclonal on immunoperoxidase staining. Seven patients relapsed at 3 to 36 months PT; of these, 5 patients remain alive at 22+ to 68+ months PT, and 2 patients died at 14 and 27 months PT. The median
progression-free survival is 36 months and median overall
survival has not yet been reached.

Epidermidis, Escherichia coli, and enterobacter in 1 patient
each. Six of the 13 patients developed acute GVHD: grade I
in 4 patients, grade II in 1 patient, and grade III in 1 patient.
Acute GVHD resolved in 3 patients with topical and/or oral
corticosteroid therapy, and in 2 patients without treatment.
A single patient developed chronic GVHD and was treated
with corticosteroids and cyclosporine for 4 months, and has
required no therapy thereafter.

Two patients developed VOD characterized by weight
gain, ascites, and liver function test abnormalities in the first
month PT. In the first patient, total bilirubin peaked at 4.3
mg/dL on day 15 PT; treatment with pentoxifylline led to
resolution of VOD and discharge at day 33 PT. The other
patient developed clinical VOD and rising total bilirubin on
day 11 PT; despite treatment with tissue plasminogen activ-
ator, heparin, pentoxifylline, and prosta glandin E1, he
expired on day 40 PT with total bilirubin of 40 mg/dL. At
postmortem examination, the liver showed signs of pro-
found venous congestion and biliary stasis and ascites was
present. Characteristic signs of GVHD in the gastrointesti-
nal tract, skin, and liver were not present, nor was there any
evidence of residual myeloma in marrow.

A third patient engrafted promptly, with granulocytes
greater than 500/µL and platelets greater than 20,000/µL at
days 17 and 19 PT, respectively. The marrow donor was her
brother who was both HLA and AB0 compatible. On day
21 PT, the patient was begun on Bactrim therapy for a uri-
inary tract infection; by day 49 PT she had developed pro-
found pancytopenia, with fewer than 100 lymphocytes/µL,
all of which were of her own type. No evidence of viral or
other infection was documented, and a trial of granulocyte
colony stimulating factor did not increase her leukocyte
counts. She therefore underwent a second allograft with her
brother's non-T-cell depleted marrow, after preparation
with cyclophosphamide 50 mg/kg on 4 consecutive days
and antithymocyte globulin. Although she engrafted
promptly with greater than 500 granulocytes/µL and un-
transfused platelets greater than 20,000/µL on days 11 and
14 PT, respectively, she died in the setting of GVHD, which
was refractory to immunosuppressive therapy including cor-
ticosteroids and cyclosporine as well as IL-1 receptor antago-
nist.

α2b IFN therapy. Of the 26 patients who underwent
autologous BMT, 13 patients received IFN: 3 patients pre-
BMT, 3 patients at the time of relapse post-BMT, 6 patients
as maintenance therapy post-BMT, and 1 patient both before BMT and as maintenance therapy post-BMT. Five patients did not receive maintenance IFN post-BMT because of low counts; of those receiving maintenance therapy, dose reduction (1 patient) or discontinuation (1 patient) was required due to pancytopenia; IFN was discontinued in an additional patient due to the development of pulmonary infiltrates. One of the 6 patients on maintenance IFN therapy has progressed.

Of the 14 patients who underwent allogeneic or syngeneic BMT, 10 patients received IFN therapy: 1 patient pre-BMT, 2 patients at the time of relapse post-BMT, and 7 patients as maintenance therapy post-BMT. Two patients did not receive IFN post-BMT because of low counts; discontinua-

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**Fig 1.** MM autologous transplant.

**Fig 2.** MM allogeneic transplant.
tion of maintenance IFN post-BMT was required in 3 patients due to the development of thrombocytopenia and fatigue. One of the 7 patients on maintenance IFN post-BMT has progressed.

**DISCUSSION**

In this study, we report the results of 40 patients with multiple myeloma who underwent high-dose chemoradiotherapy and either anti-B-cell MoAb-treated autologous BMT or anti-T-cell MoAb-treated allogeneic BMT. The majority of patients had advanced Durie-Salmon stage myeloma, had sensitive relapsed myeloma and were heavily pretreated with chemotherapy; 17 had received prior radiotherapy. At the time of BMT, all patients demonstrated good performance status with Karnofsky score of 80% or greater and had less than 10% marrow tumor cells; 34 patients had residual monoclonal marrow plasma cells and 38 patients had paraprotein. There were 18 CRs, 18 partial responses, 1 nonresponse, and 3 toxic deaths. Less than 5% polyclonal marrow plasma cells were noted in all responders after BMT. As of November 1, 1992 with 24 months median follow-up for survival among the autologous BMT cases, 16 of 26 patients are alive free from progression at 2+ to 55+ months PT; of these, 5 patients remain in CR at 6+ to 55+ months PT. With 24 months median follow-up for survival among the allogeneic and syngeneic BMT cases, 8 of 14 patients are alive free from progression at 8+ to 34+ months PT; of these, 5 patients remain in CR at 8+ to 34+ months PT. Although this therapy has achieved high response rates and prolonged progression-free survival in some patients and proven to have acceptable toxicity, relapses post-BMT suggest that such treatment strategies should be used earlier in the disease course and their efficacy compared with that of conventional chemotherapy in a randomized trial.

Melphalan and prednisone therapy can result in response rates of 50% to 60% and a median survival of 48 months; and to date it remains controversial as to whether combination chemotherapy programs have improved on this outcome.1,4-7 Once patients become refractory to initial therapies, salvage therapies such as vincristine, doxorubicin, and dexamethasone35 can achieve response rates of 50% to 75%; however, these responses are uncommonly either complete or durable. High-dose melphalan with or without total body irradiation and hematopoietic stem cell support was initially used by McElwain et al.27,28 This strategy has achieved responses even in the setting of patients refractory to initial therapy.16-19 However, in most studies, significant relapse-free survival was noted only in a minority of patients with sensitive disease, and those patients with resistant relapse or with a combination of risk factors (ie, advanced tumor burden, absence of IgG isotype)30 did particularly poorly. Nonetheless, as is true in B-cell non-Hodgkin’s lymphomas (NHL), high-dose therapy followed by autologous BMT is the only strategy to have achieved significant relapse-free survival. For example, at our institute, MoAb-purged autologous BMT for patients with relapsed B- and T-cell NHL sensitive to chemotherapy has resulted in 40% to 50% relapse-free survival at 2 to 3 years.7,49 Although follow-up is short and long-term outcome remains to be determined, the current study of either MoAb-purged autologous or allogeneic BMT in myeloma sensitive to therapy has achieved significant overall and relapse-free survivals (Figs 1 and 2). However, only 5 of 26 patients undergoing autologous BMT and 5 of 14 patients undergoing allogeneic BMT remain in CR at 6+ to 55+ and 8+ to 34+ months PT, respectively. In the largest reported series to date of high-dose therapy followed by allogeneic BMT in myeloma, median relapse-free survival for 37 of 90 (41%) patients who entered complete remission was 48 months.23 In this study, those patients with sensitive disease and who were less heavily pretreated achieved the highest response rates and prolonged progression-free survival. These studies suggest, as has occurred in leukemias and lymphomas, that high-dose approaches should be evaluated earlier in the disease, before the emergence of drug resistance and refractory disease.

An additional impetus for using high-dose approaches earlier in the disease course, now that toxicities of such approaches have proven to be tolerable, relates to the quality of autologous hematopoietic stem cells and related speed and completeness of hematologic recovery after high-dose therapies. For example, Jagannath et al have attempted PBSC collection in 75 previously treated patients with myeloma after the administration of high-dose cyclophosphamide with or without granulocyte-macrophage colony-stimulating factor (GM-CSF).39 Among 72 patients undergoing PBSC apheresis, good mobilization (>50 colony-forming units GM per 10⁵ mononuclear cells) was achieved when prior chemotherapy did not exceed 1 year and when GM-CSF was used post–high-dose cyclophosphamide; similarly, rapid platelet recovery (to 50,000/μL) was associated with good PBSC mobilization. In the present study of high-dose chemoradiotherapy followed by autologous BMT in heavily pretreated patients with myeloma, delayed engraftment was also noted; greater than 500 granulocytes/μL and greater than 20,000/μL platelets were noted as long as 46 days and 175 days PT, respectively, and 2 patients did not achieve platelet transfusion independence at the time of their deaths at 2 and 6 months PT. Moreover, it was not possible to treat all patients with IFN post-BMT due to related myelosuppression. Treatment of patients with high-dose approaches earlier in their disease course may therefore be useful not only for the avoidance of drug resistance, but also to assure preservation of sufficient hematopoietic stem cells to permit rapid hematologic recovery and low-treatment-related morbidity and mortality.

Several investigators have used intensive treatment of multiple myeloma supported by autologous BM and/or PBSC transplantation as initial therapy in myeloma.18,28,37,38 For example, Gore et al treated 50 patients with myeloma with repeated cycles of 4-day infusions with vincristine, doxorubicin, and methylprednisolone followed by high-dose melphalan, with autologous BMT where possible.28 The overall response rate was 74%, with 50% complete hematologic and biochemical remissions. More recently, these investigators have demonstrated that patients who receive maintenance IFN post-autologous BMT have prolonged median progression-free survival (39 months) compared
with those patients who are not treated with IFN (27 months) \( P < .025 \).\(^{50}\) Attal et al recently treated 35 patients with myeloma with repeated cycles of either vincristine, doxorubicin, and dexamethasone, or vincristine, melphalan, cyclophosphamide, and prednisone until plateau phase was achieved.\(^ {34}\) High-dose melphalan, and TBI followed by autologous BMT and maintenance IFN resulted in 43% and 40% complete and partial responses, respectively. The 33-month post-BMT probability of progression-free survival was 85% for patients in complete and 24% for patients in partial response. The 42-month post-diagnosis probability of survival was 81%. These and other similar studies\(^ {37}\) suggest that high-dose approaches early in the disease course can achieve high response rates and that therapeutic interventions post-BMT, such as IFN maintenance, may be better tolerated by such patients than in more heavily pretreated patients. They provide the basis on which a randomized trial comparing high-dose versus conventional-dose chemoradiotherapy for patients with untreated myeloma can be based.

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