CONCISE REPORT

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

By Bart Barlogie, Raymond Alexanian, Karel A. Dicke, Gunar Zagars, Gary Spitzer, Sundar Jagannath, and Leonard Horwitz

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.

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 program6 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 MP-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.9

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

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 because of 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 2-1/2 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 x 10^10 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). Anticoagulation 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.

From the Department of Hematology, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston.


Supported in part by Grants No. CA 37161 and CA23077 from the National Institutes of Health and the Cullen Trust Foundation.

Address reprint requests to Bart Barlogie, MD, M.D. Anderson Hospital and Tumor Institute, Department of Hematology, 1515 Holcombe Blvd, Box 55, Houston, TX 77030.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

© 1987 by Grune & Stratton, Inc.
Table 1. Patient Characteristics and Response to TBI/High Dose Melphalan

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

*Tumor mass: I, intermediate; H, high (Durie-Salmon).
†Performance status, Zubrod scale.
‡Using DNA-Ctg flow cytometry.
§Plasma cells, nonsecretory myeloma.
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. A third relapse. This 50-year-old patient had responded previously but achieved even greater cytoreduction after HDM/TBI.

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; these five patients eventually achieved normal cellularity and differential counts, respectively, without detectable monoclonal plasmacytosis on flow cytometry. One patient (BL) remained thrombocytopenic at a level of 50,000/μL 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/μL and severe thrombocytopenia <10,000/μL.

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). In contrast, and stressing the cytoreductive potency of added TBI in plasma cell myeloma, 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-versus-host disease with allogeneic BMT in older patients, marrow-ablative therapy has not been explored systematically in multiple myeloma. Cyclophosphamide/TBI and modifications with
syngeneic or allogeneic BMT have been effective in about a
dozen patients, many of whom still had drug-responsive
myeloma.\textsuperscript{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 induct-
ion 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.\textsuperscript{20,21} 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-vs-host
disease, most myeloma patients are candidates for autolo-
gous 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 hemat-
ologic 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.\textsuperscript{21} In addition, the terminally differen-
tiated B cells that comprise this tumor have an unusually low
in vitro, and perhaps in vivo, cloning efficiency.\textsuperscript{22} Thus, a
selective growth advantage of normal hematopoietic 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 hematopoietic engraftment is not compromised.
The effectiveness of TBI/HDM, when supported by autolo-
gous 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.

REFERENCES

1. Barlogie B, Smith L, Alexanian R: Effective treatment of
advanced multiple myeloma refractory to alkylating agents. N Engl
J Med 310:1333, 1984
2. Alexanian R, Barlogie B, Dixon D: High-dose glucocorticoid
for plasma-cell leukaemia and myeloma. Lancet i:822, 1983
5. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R: High-
dose melphalan with autologous bone marrow transplantation for
Med J 2:325, 1971
7. Knowling M, Harwood A, Bergsagel DR: A comparison of
extramedullary plasmacytomas with multiple and solitary plasma
8. Rowland CG, Garrett MJ, Crowley FA: Half body radiation in
9. Rostom AV, O'Callah SM, Fokes A: Systemic irradiation in
10. McLaughlin P, Alexanian R: Myeloma protein kinetics fol-
lowing chemotherapy. Blood 60:851, 1982
Drewinko B: Marrow cytometry and prognosis in myeloma. JCI
72:853, 1983
T: Cytoplasmic immunoglobulin content in multiple myeloma. JCI
76:765-769, 1985
marrow transplantation in multiple myeloma: A case report with
chemoradiotherapy and BMT in the management of multiple myelo-
ma. Italian Experience. Bone Marrow Transplant 1:194, 1986
15. Ozer H, Han T, Nussbaum-Blumenson A, Henderson ES,
Fitzpatrick J, Higby DJ: Allogeneic bone marrow transplantation and
idiotype monitoring in multiple myeloma. Am Assoc Cancer Res
25:161, 1984
16. Osserman EF, DiRe LB, DiRe J, Sherman WH, Hersman
JA, Storb R: Identical twin marrow transplantation in multiple
17. Fefer A: Current status of syngeneic marrow transplantation
18. Kyle RA, Greipp PR, Gertz MA: Treatment of refractory
multiple myeloma and considerations for future therapy. Semin
Oncol 13:326, 1986
Lucarelli G, Michallet M, Reiffers J, Ringden O, van Lint MT,
Vernant JP, Zwaan FE: Bone marrow transplantation in multiple
myeloma: Report from the European Cooperative Group for Bone
20. Hall R, Barlogie B, Alexanian R: High dose alkylating agent
22. Salmon SE: In vitro cloning and chemosensitivity of human
myeloma stem cells. Clin Haematol 47, 1982
High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma

B Barlogie, R Alexanian, KA Dicke, G Zagars, G Spitzer, S Jagannath and L Horwitz