Autologous Bone Marrow Transplantation in Multiple Myeloma: Identification of Prognostic Factors

By Sundar Jagannath, Bart Barlogie, Karel Dicke, Raymond Alexanian, Gunnar Zagars, Bruce Cheson, Frederick C. Lemaistre, Leslie Smallwood, Kimberly Pruitt, and Dennis O. Dixon

Multiple myeloma remains a universally fatal malignancy with a median survival time not exceeding 3 years. A clinical trial was undertaken to determine feasibility and efficacy of marrow-ablative chemoradiotherapy supported by unpurged autologous bone marrow (ABMT) and to define prognostic variables. Total body irradiation and either melphalan or thiotepa were administered to 55 patients (median age 53 years; range 20 to 66 years). The group of 21 patients with resistance to standard melphalan-prednisone and to continuous infusions of vincristine and Adriamycin with high dose dexamethasone (VAD) included 7 with primary unresponsive disease and 14 with resistant relapse; among the 34 patients achieving remission with the VAD regimen, 14 were in first and 20 in a subsequent remission. Marked cytoreduction by \( \geq 75\% \) was observed among all 21 patients with refractory myeloma, whereas further cytoreduction of this magnitude was noted in only 56% of the 34 patients already in remission after VAD. Five of the 6 early deaths among all 55 patients occurred in the 14 patients with resistant relapse, none of whom achieved complete remission and who, as a group, had median durations of relapse-free and overall survival of only 8 and 7 months, respectively. Among the 41 remaining patients, there was only one early death, and 27% achieved complete remission including a 36% incidence among the 14 patients treated in first remission; their projected 4-year survival rate was 82% regardless of their disease status (first or later remission or primary resistance). When information about sensitivity to prior therapy is unavailable, the presence before ABMT of both high beta-2-microglobulin levels (\( \geq 3 \text{ mg/L} \)) and non-IgG isotype helped identify 9 among the 55 patients with a very poor prognosis: all 8 responders relapsed within 9 months, and 8 patients died within 15 months. By contrast, a 4-year projected survival rate of over 70% for the other patients (about 80% of this series) justifies further investigation of this novel treatment approach in comparison with standard dose regimens. Our results indicate that marrow-ablative therapy cannot be recommended for myeloma patients with resistant relapse or those with a combination of risk factors (advanced tumor burden, absence of IgG isotype). The apparent lack of an adverse effect of even marked plasmacytosis in autografts (up to 30%) emphasizes the need for better cytoreduction rather than bone marrow purging.

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THE PROGNOSIS OF patients with multiple myeloma (MM) has not changed markedly since the introduction of melphalan and prednisone (MP) about 25 years ago.\(^1,2\) Although the role of added cytotoxic agents such as Adriamycin and nitrosoureas has remained controversial,\(^3\) the recently introduced biological agent, alpha-interferon, seems to increase response rates\(^4\) and prolong remission and survival.\(^5,6\) Because of their advanced age and increased susceptibility to infections, patients with MM have generally not been considered for high dose cytotoxic regimens that have improved survival and cure rates in other drug-sensitive malignancies. However, when supported by autologous bone marrow grafts (BMT), high dose melphalan and even added total body irradiation (TBI) can be administered relatively safely to elderly patients.\(^7\) Our pilot trial in 7 patients with advanced and refractory disease generated considerable interest in such marrow-ablative regimens for MM so that, worldwide, over 200 patients have already received autologous hemopoietic stem cells in support of high dose therapy regimens. Except for a recent report on 50 newly diagnosed patients by Gore et al, most trials included fewer than 20 patients, in various stages of disease.\(^8\) While interest in intensive therapy requiring hemopoietic stem cell support is still growing, guidelines have not yet been developed as to which patients may benefit from this treatment approach. Such information appears crucial for the design of prospective trials comparing standard and high dose regimens. Experience with high dose chemoradiotherapy in 55 patients in early and late phases of their MM helped us identify risk factors according to which future patients can be stratified.

MATERIALS AND METHODS

Patients. Fifty-five patients with MM were treated at a single institution (M.D. Anderson Cancer Center, Houston, TX) with melphalan and TBI, and thiotepa was substituted for melphalan in 18 patients when the intravenous formulation of melphalan was temporarily unavailable (Table 1). Their median age was 53 years (range 20 to 66 years), and 22% were older than 60 years. Fifty-five percent of patients had IgG myeloma. Once the relative safety and efficacy of such high dose therapy had been established in 21 patients with resistance to standard MP or similar regimens (with added cyclophosphamide, nitrosourea or doxorubicin) and to vincristine-Adriamycin-dexamethasone (VAD),\(^2\) this program was also evaluated in 34 patients who had achieved remission, either after initial induction treatment with 4 to 6 cycles of VAD (6 patients with intermediate and 8 with high tumor mass in the Durie-Salmon staging system) or after effective salvage therapy with VAD (20 patients in later remissions) (Table 1). As expected, beta-2-microglobulin (B2M) levels were elevated more frequently among patients who had achieved remission, either after initial induction treatment with 4 to 6 cycles of VAD (6 patients with intermediate and 8 with high tumor mass in the Durie-Salmon staging system) or after effective salvage therapy with VAD (20 patients in later remissions) (Table 1). As expected, beta-2-microglobulin (B2M) levels were elevated more frequently among
AUTOLOGOUS BONE MARROW TRANSPLANTATION IN MM

Patients receiving high dose therapy for consolidation of their remissions included age up to 70 years, adequate renal (serum creatinine <2mg%) and liver function (bilirubin <2 mg%, SGPT <2 x normal), as well as normal cardiac and pulmonary functions (systolic ejection fraction of >50% and carbon monoxide diffusion capacity >50%). In case of salvage therapy, bone marrow autografts could contain as many as 30% plasma cells (range 1% to 30%, median 6%). While there was a requirement prior to bone marrow harvest that plasma cells not exceed 5% in patients receiving consolidation therapy, examination of harvested marrow revealed 12 cases with more than 5% and 5 with more than 10% plasma cells (see Table 1). On a per-kilogram body weight basis, at least 1 x 10^8 mononuclear cells and 1.5 x 10^6 CFU-GM were required. Autologous marrow was cryopreserved in dimethylsulfoxide for periods ranging from 1 to 39 months (median 2 months). Marrow autografts had been obtained in remission among all 34 patients receiving chemoradiotherapy for remission consolidation but in only 8 patients who later received such high dose therapy for resistant myeloma.

The treatment regimen consisted of either melphalan (140 mg/m^2 [body surface area] IV over 20 to 30 minutes) or thiotepa (750 mg/m^2 in 3 divided doses 12 hours apart) followed within 2 days by TBI (total of 850 cGy in 5 equal doses of 170 cGy in 3 days). An initially higher dose of thiotepa (900 mg/m^2) was abandoned because of excessive mucositis and gastrointestinal toxicity in the first 3 patients treated. Autologous bone marrow was infused intravenously within 24 hours after completion of TBI. Patients had to provide written informed consent to the experimental treatment in keeping with hospital policies. When available and patients' performance permitted appropriate self-care, therapy was administered under strict gnotobiotic conditions in a laminar air flow room (41 patients); the remaining patients were treated in a private room on a regular hospital ward. Antibiotic prophylaxis involved trimethoprim-sulfamethoxazole and ketoconazole as well as acyclovir. Blood products and broad spectrum antibiotics were given as needed. Laboratory monitoring was extensive and frequent to determine antitumor effect and toxicities.

Response. Identical response criteria were applied both for standard dose chemotherapy before BMT and for high dose therapy regimens. Remissions were defined as ≥75% tumor cytoreduction with disappearance of Bence-Jones proteinuria, resolution of marrow plasmacytosis to less than 5% and disappearance of soft tissue lesions. Complete remission required, in addition, the absence of monoclonal gammopathy on immunofixation analysis of both serum and urine. Despite attaining tumor cytoreduction by ≥75%, all patients dying within 2 months of starting therapy (early deaths) were considered as treatment failures and were excluded from the analysis of relapse-free survival. For patients with sensitive disease receiving BMT-supported consolidation therapy in remission, complete response rates were computed before and after high dose therapy. Among responding patients surviving at least 2 months after BMT, relapse-free survival was defined as the time from treatment until either the recurrence of monoclonal gammopathy, doubling of lowest tumor mass, or increase to ≥25% of pre-treatment mass, whichever occurred first. When high dose therapy was applied in remission, all patients except one early death were included as relapse-free. Survival was defined as the time from treatment to death.

A variety of regimens was used for relapse from marrow-supported high dose therapy. These included high dose dexamethasone pulse (11); interferon-alpha; VAD; a combination of etoposide, dexamethasone, cisplatin and cis-platinum (EDAP); as well as repeated marrow-ablative therapy.

Statistical analysis. Statistical methods included chi-square tests for comparison of rates; Kaplan-Meier estimates of relapse-free survival and survival curves; and generalized Wilcoxon tests for comparison of curves. Variables examined before high dose therapy included age, performance status, tumor-mass features, B2M, LDH, Ig isotype, prior drug resistance, melphalan versus thiotepa, plasmacytosis in marrow autografts, and location of treatment (laminar air flow unit versus private hospital room). Resistance to therapy was further divided according to whether patients had never responded (primary resistance) or had relapsed from a previous remission and were no longer sensitive to VAD (resistant relapse).

RESULTS

High dose chemoradiotherapy affected marked cytoreduction by ≥75% in all 21 patients with VAD-refractory MM including 5 patients who died within 2 months from therapy; in contrast, only 56% of the 34 patients already in remission after VAD achieved further tumor cytoreduction of such magnitude. Tumor halving occurred after a median of only 9 days.

Early mortality was highest among the 14 patients with resistant relapse (36%), none of whom achieved complete remission; their median relapse-free and overall survival durations were short at 8 and 7 months, respectively (Table 2). There was only one early death among the remaining 41 patients (2%), and the frequency of complete remission was 27% and did not differ markedly among the 3 subgroups of patients with primary drug resistance and those treated in first or subsequent remission. Median durations of relapse-free and overall survival for the 41 patients were 20 and 53 months, respectively, and did not differ markedly among the 3 subgroups.

Because of their similar prognoses, remission patients and those with primary refractory myeloma were combined as one group (41 patients) in order to define prognostic parameters before high dose therapy. Low B2M levels (≤2.5 mg/L)
And IgG kappa isotype were the only parameters significantly associated with longer relapse-free and overall survival durations (Table 3). The presence of both high B2M levels and absence of IgG kappa defined a small high-risk subgroup of 6 patients (among the 41 more favorable patients) with as poor a prognosis as had been observed among those with resistant relapse (Table 3 and Fig 1). These poor risk features, especially high B2M >3 mg/L and absence of IgG (rather than IgG kappa) isotype, were also represented more prominently among patients with resistant relapse than in any other subgroup (86% versus 46%, P = .02).

Since information on sensitivity to prior therapy is often incomplete, a risk assessment based entirely on readily available laboratory parameters is highly desirable. In view of comparably poor prognoses in patients with resistant relapse and with high B2M without IgG isotype among the more favorable group, the prognostic importance of the concurrent presence of these 2 features before high dose therapy was examined among all 55 patients treated (Fig 2). Thus, 9 patients were identified with a significantly shorter median survival of 10 months compared with a projected survival of 18 months in all patients treated (Fig 2). Surprisingly, the extent of plasmacytosis in autografts did not affect remission or survival times in any of the above subgroups. Median relapse-free and overall survival after TBI with thiotepa were 7 and 15 months compared with 16+ and 47+ months after treatment with TBI and melphalan (P = .1).

Table 3 summarizes, in univariate fashion, the pre-treatment variables associated with poor clinical outcome. When information on response to previous therapy is available, the presence of resistant relapse conferred a high early mortality, low complete remission as well as short relapse-free and overall survival durations. In the absence of such detailed knowledge about patients' previous response history, elevated levels of B2M seem to be most closely linked to short remissions and survival times. Considering the potentially lethal toxicity of high dose therapy, segregation of patients with a very poor prognosis is highly desirable; thus, the concomitant presence of B2M elevation and non-IgG isotype defined a small subset of 9 patients with median durations of relapse-free and overall survival of 5 and 10 months respectively; conversely, the remaining 46 patients enjoyed a sufficiently good prognosis for such high dose regimens to be explored further.

The most serious toxicity from TBI-alkylating agent therapy consisted of life-threatening infections during agranulocytosis. Pneumonia occurred in 38% of patients with VAD-refractory but in only 10% with VAD-sensitive disease (P = .05), although there was no difference in the speed of hematologic recovery between the 2 groups. With the exception of patients presenting with resistant relapse, faster hematologic recovery was observed when greater quantities of marrow progenitor cells (CFU-GM) were infused (Table 5).
Extramedullary toxicity was more pronounced with thiotepa than with melphalan and TBI. Thus, 70-80% of all patients receiving thiotepa-TBI experienced severe and protracted stomatitis, esophagitis, and diarrhea, whereas such toxicities occurred in only 20% of those treated with melphalan (P < .001).

Reinduction of remission after relapse from high dose therapy was successful in 50% of patients, whether or not they relapsed after consolidation or salvage therapy (Table 6). Three of ten patients responded to high dose dexamethasone alone or with added interferon; VAD was effective in 7 of 15 patients treated. Subsequent survival was not influenced by the type of salvage regimen employed and increased markedly with the duration of posttransplant remissions, so that 9 of 10 patients relapsing more than 9 months after BMT remain alive compared to a median post-BMT survival of only 9 months when relapses had occurred within 9 months after high dose therapy (P = .04).

Estimates of total survival from initial therapy are biased by patient selection. With a median follow-up of about 2 years among the 34 patients treated in remission, their projected 5-year survival rate was 80%. The median survival of the 21 patients with refractory myeloma was 40 months.

Fig 1. Relapse-free survival (A) and overall survival (B) were superior among patients who did not have both high B2M levels (>3 mg/L) and IgA or Bence-Jones myeloma. Thus, if information on previous drug sensitivity is unavailable, these two parameters can be used for risk assessment when considering high dose therapy with autologous bone marrow transplantation for myeloma.

Fig 2. Relapse-free survival (A) and overall survival (B) were superior among patients who did not have both high B2M levels (>3 mg/L) and IgA or Bence-Jones myeloma. Thus, if information on previous drug sensitivity is unavailable, these two parameters can be used for risk assessment when considering high dose therapy with autologous bone marrow transplantation for myeloma.

DISCUSSION

In recent years, new insights into the biology of MM have been gained. Advances in therapy include the development of the VAD regimen, the discovery of interferon's activity mainly in low-tumor mass disease, and the demonstration that marrow-ablative therapy is feasible and has activity in refractory MM. A survey of the recent literature showed that over 200 patients with MM have been treated with high dose therapy and autologous marrow and/or blood stem cell support in addition to over 100 patients who have received allogeneic BMT in various stages of their disease, mainly as part of the European bone marrow transplant program. With allogeneic BMT, approximately 40% of patients achieved complete remission, one-third died from transplant-related complications, and about 35% showed no evidence of disease progression (although frequently still disease activity) at about 3 years after BMT.

The autologous transplantation experience can be divided into 3 groups of trials using unpurged or purged bone marrow or peripheral blood stem cells. The largest experience was published recently by Gore et al on 50 newly diagnosed patients receiving the VAMP regimen (substituting dexamethasone in VAD with methylprednisolone). The 28 patients achieving reduction in marrow plasmacytosis to 30% or less
Table 4. Univariate Analysis of Prognostic Parameters for Clinical Outcome

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Unfavorable Variable</th>
<th>Absent (N)</th>
<th>Present (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Death</td>
<td>Resistant Relapse</td>
<td>.003</td>
<td>2 (41)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>Resistant Relapse</td>
<td>.08</td>
<td>2 (41)</td>
</tr>
<tr>
<td>Relapse-Free Survival</td>
<td>B2M &gt;2.5 mg/L</td>
<td>.0001</td>
<td>20 (26)</td>
</tr>
<tr>
<td></td>
<td>B2M &gt;3 mg/L and non-IgG</td>
<td>.0001</td>
<td>19 (41)</td>
</tr>
<tr>
<td></td>
<td>Resistant Relapse</td>
<td>.01</td>
<td>19 (40)</td>
</tr>
<tr>
<td></td>
<td>Non-IgG</td>
<td>.02</td>
<td>19 (27)</td>
</tr>
<tr>
<td></td>
<td>Age &gt;50 y</td>
<td>.06</td>
<td>16 (22)</td>
</tr>
<tr>
<td></td>
<td>Performance Status &gt;1</td>
<td>.09</td>
<td>16 (43)</td>
</tr>
<tr>
<td>Survival</td>
<td>Resistant Relapse</td>
<td>.0001</td>
<td>53 (41)</td>
</tr>
<tr>
<td></td>
<td>B2M &gt;3 mg/L and non-IgG</td>
<td>.0007</td>
<td>53 (46)</td>
</tr>
<tr>
<td></td>
<td>B2M &gt;2.5 mg/L</td>
<td>.001</td>
<td>43 (28)</td>
</tr>
<tr>
<td></td>
<td>Performance Status &gt;1</td>
<td>.007</td>
<td>43 (46)</td>
</tr>
<tr>
<td></td>
<td>Non-IgG</td>
<td>.03</td>
<td>53 (30)</td>
</tr>
<tr>
<td></td>
<td>Age &gt;50 years</td>
<td>.08</td>
<td>53 (24)</td>
</tr>
</tbody>
</table>

*Percent.  
†Median months.

received a high dose of melphalan at 200 mg/m² with unpurged marrow support; a lower dose of 140 mg/m² without marrow support was employed for 11 patients not achieving such reduction in plasmacytosis. Fifty percent achieved complete remission (disappearance of monoclonal gammapathy on standard protein electrophoresis). With a median follow-up of 1.2 years (range 0.6 to 3 years), the projected survival rate 3 years after VAMP induction therapy was almost 80%; however, 10 of 12 partial responders and 5 of 25 patients achieving complete remission have relapsed.

The current study confirms the feasibility of administering marrow-ablative cytotoxic therapy with TBI to elderly patients with MM when supported by autologous BMT. All 21 patients with refractory MM achieved marked cytodestruction by ≥75% compared with only 56% among those already in remission, contrasting with complete remission rates of 10% and almost 30%, respectively, in these two groups.

The inclusion of patients in different stages of their disease, who could be grouped according to their responsiveness to the VAD regimen, led to the identification of prognostic variables which deserve consideration in future trials. Similar to experience with high dose therapy trials in lymphoma, 24 patients with resistant relapse from MM did not benefit from this treatment approach, because of poor tolerance, prevalence of 3 years after VAMP induction therapy was almost 80%; however, 10 of 12 partial responders and 5 of 25 patients achieving complete remission have relapsed.

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In addition, 27% of the remaining 41 patients achieved complete remission; the highest incidence of 36% was observed among patients treated in first remission, similar to the 50% reported by Gore et al in comparable patients, especially when one considers that more stringent criteria were applied in our study. Surprising was the fact that the 7 patients with primary refractory myeloma fared so well; frequency of complete remission and duration of disease control were comparable to results obtained in patients treated in remission, suggesting similar sensitivities to high dose chemoradiotherapy. Although relatively more resistant to standard dose regimens than patients achieving remissions on VAD, those with primary refractory MM may have tumor stem cells with preserved sensitivity to the high dose chemoradiotherapy regimen that probably targets tumor cells at a much earlier stage of maturation than VAD.

In addition to the poor risk group of patients with resistant relapse, the combination of more advanced tumor burden and absence of IgG kappa isotype identified an additional subgroup of patients with poor prognosis. While not accounting entirely for their poor prognosis, these features were also more prevalent among patients with resistant relapse. As a result, these two features defined a small but remarkably

Table 5. Hematologic Recovery According to Quantity of Marrow Progenitor Cells (CFU-GM) Administered

<table>
<thead>
<tr>
<th>CFU-GM/kg x 10⁴</th>
<th>Median Days To Granulocytes &gt;500/μL</th>
<th>Platelets &gt;50,000/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistant Relapse</td>
<td>Other</td>
</tr>
<tr>
<td>&lt;1</td>
<td>21 (8)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>1-5</td>
<td>29 (5)</td>
<td>20 (19)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>32 (1)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>P</td>
<td>.7</td>
<td>.01</td>
</tr>
</tbody>
</table>

(1) Denotes number of patients.
Table 6. Salvage Therapy After Relapse From High Dose Therapy With Autologous Bone Marrow Transplant (ABMT)

<table>
<thead>
<tr>
<th>Initial Regimen</th>
<th>Subsequent Regimen</th>
<th>N</th>
<th>Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-Dex None</td>
<td>High-dose melphalan (100 mg/mojL2) without BMT</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>VAD</td>
<td>BU-Cy + Allogeneic BMT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>VAD</td>
<td>EDAP</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>VAD</td>
<td>IFN-Dex None</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>24</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: IFN; interferon-alpha 3 to 9 x 10^9 U/mojL2 daily or every other day; Dex; dexamethasone 40 mg on days 1-4, 9-12, 17-20 (see ref 11); VAD; vincristine-adriamycin-dexamethasone (see ref 9); BU-Cy; busulfan 16 mg/kg and cyclophosphamide 120 mg/kg; EDAP; etoposide, dexamethasone, cytosine-arabinoside and cis-platinum (see ref 12).

homogeneous group of patients with very short remissions and survival times, who should be excluded from future high dose therapy trials. The other 80% of patients had a favorable prognosis, with a projected survival rate of 72% at 4 years. In considering patients for chemoradiotherapy and autologous bone marrow transplantation, information on previous therapy and treatment response is often incomplete, so that an entirely laboratory-based risk assessment is desirable. Superior results can be anticipated among patients with low B2M before ABMT or with an IgG isotype. The association of greater drug resistance with IgA and only light chain MM has not been observed routinely with standard dose regimens and its mechanism remains elusive.

Surprisingly, a greater extent of plasmacytosis in marrow autografts was not harmful. Thus, under the present trial conditions, the presence of up to 30% mainly terminally differentiated tumor cells was prognostically unimportant in a disease in which recent evidence points to a tumor stem cell compartment at a much earlier stage of differentiation.33 Indeed, preliminary data from small recent trials that included marrow purging indicate that relapses do occur within one year of transplantation.19,20 Because of the presence in peripheral blood of aneuploid plasma cells26 and of earlier tumor cell progenitors,27 blood may not be superior to bone marrow as a source of normal stem cells in patients with MM.

While the origin of relapse after ABMT for marrow-derived malignancies is difficult to assess, the observation of early relapse despite marrow purging justifies our efforts to attempt better pre-transplant cytoreduction using truly non-cross-resistant regimens such as VAD, intermediate doses of intravenous melphalan plus GM-CSF,26 and combinations with etoposide, cisplatin, ARA-C and dexamethasone (EDAP).13 Marrow ablative therapy can perhaps be intensified further by repeated applications, which seem to be more feasible with melphalan alone at a higher dose of 200 mg/m2, as used by Gore et al,8 rather than with added TBI.7 The notion of more complete and durable remissions, even in resistant myeloma, after allogeneic compared to autologous BMT in support of similar TBI-containing conditioning regimens24 raises the issue of graft-versus-tumor effect also in MM, which is well documented in similar clinical trials for leukemia.29 These results also indicate that autologous BMT trials with curative intent require more intensive cytoreduction to offset the lack of graft-versus-tumor effect with allogeneic BMT. The ultimate benefit of such total therapy for MM requires comparative clinical trials with the best standard dose regimens.

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