Intensive Combined Therapy for Previously Untreated Aggressive Myeloma

By Michel Attal, Françoise Huguet, Daniel Schlaifer, Catherine Payen, Michel Laroche, Bernard Fournie, Bernard Mazieres, Jacques Pris, and Guy Laurent

A trial was initiated to determine the feasibility and efficacy of a three-phase treatment including: (1) induction chemotherapy (IC); (2) high-dose melphalan with total body irradiation supported by unpurged autologous bone marrow transplantation (ABMT); and (3) interferon (IFN) α maintenance treatment, in previously untreated aggressive myeloma. Thirty-five consecutive patients, ages under 65 years, were enrolled. Initial induction therapy was randomized between the VAD regimen (vincristine, doxorubicin, dexamethasone) or the VMCP regimen (vincristine, melphalan, cyclophosphamide, prednisone) that were found to give similar results as IC. Thirty-one of 35 (89%) patients, with good performance status and normal renal function after IC, received ABMT. IFN α was started soon after ABMT and was well tolerated.

For the past 25 years, intermittent melphalan-prednisone has been the standard treatment for multiple myeloma (MM). Extensive clinical trials with other drug combinations have been made with major improvements. Thus, median survival does not usually exceed 2 to 3 years with conventional chemotherapy.1

High-dose therapy has been developed to improve survival of aggressive myeloma.2 Although a high response rate was observed in both previously untreated and chemoresistant patients, severe life-threatening hematologic toxicity occurred in these patients.3 Various hematopoietic stem cell supportive measures have been investigated to decrease this toxicity. Allogeneic bone marrow transplantation can only be applied to young patients with HLA-identical siblings and carries the risk of graft-versus-host disease, which increases with the patient's age.4 Autologous transplantation with unpurged6 or purged7 bone marrow or peripheral stem cells8,9 was shown to virtually eliminate early mortality by reducing the duration of cytopenia. Furthermore, Barlogie et al10 demonstrated that high-dose melphalan (HDM), even with added total body irradiation (TBI), could be administered relatively safely to elderly patients when supported by autologous bone marrow transplantation (ABMT). As a result of this better supportive care, an increasing number of patients with MM are now treated with high-dose therapy supported by autologous hematopoietic stem cells.9 The impact of such strategies on overall survival in MM remains difficult to assess because most trials have included small number of patients at various stages of the disease and used different preparative regimens.7 Thus, studies on previously untreated consecutive patients are crucial for the design of future prospective trials comparing standard and high-dose therapies. The only study fulfilling these criteria has been reported by Gore et al.11 In this study, a 50% rate of complete response was obtained after sequential therapy including induction chemotherapy (IC) followed by ABMT prepared with HDM. However, the remissions were not durable and the median survival was 3.5 years.12

To improve the duration of response observed after HDM, new approaches are being developed.3 Barlogie et al13 showed that the combination of TBI and HDM with ABMT support was more effective that HDM alone. On the other hand, recombinant interferon α (IFN α) was found to increase the duration of response after IC.14,15 Thus, it was reasonable to speculate that a three-phase treatment including IC, ABMT prepared with a melphalan-TBI regimen, and IFN α maintenance therapy could not only increase response rate but also response duration, and ultimately survival. We have recently reported encouraging results from a study that analyzed the duration of response and the tolerance of IFN α maintenance therapy after ABMT in patients referred to our unit for BMT after first response to IC.16 However, because of patient selection, this study did not enable us to analyze the overall feasibility of such combined intensive treatment, as well as its possible influence on survival from diagnosis, in unselected aggressive myeloma.

We now report the results of a prospective trial that was aimed to address these crucial issues. Thirty-five consecutively untreated patients, ages under 65 years with high tumor mass MM, were enrolled. Patients were intended for receiving the following three-phase treatment: VAD (vincristine, doxorubicin, dexamethasone) or VMCP (vincristine, melphalan, cyclophosphamide, prednisone) as initial therapy, then ABMT prepared with HDM and TBI, followed by IFN α maintenance treatment.

Patients and Methods

Requirements for patients' enrollment. Between February 1988 and August 1990, all previously untreated patients ages 65 years or less, with Durie-Salmon (DS) stage III multiple myeloma, admitted to the department of hematology of Purpan Hospital, were
The main clinical characteristics are detailed in Table 1. Mean age was 53.8 years (range 35 to 65). There were 22 men and 13 women. Patients were categorized according to their M-protein (IgG/K: 14 cases; IgG/A: 6 cases; IgA/K: 6 cases; IgA/A: 5 cases; BJK: 3 cases; BJ: 1 case) and according to DS staging (III A: 28 cases; III B: 7 cases). All patients had pretreatment serum β2-microglobulin measured: 10 (29%) had levels above 6 mg/L, 11 (31%) had 4 to 6 mg/L, and 14 (40%) had less than 4 mg/L.

Study design. At the time of diagnosis, patients were randomized to receive VMCP (vincristine: 1 mg, intravenously [IV], day 1; melphalan: 5 mg/m²/d, orally, days 1 through 4; cyclophosphamide: 100 mg/m²/d, orally, days 1 through 4) or VAD (continuous intravenous infusion of vincristine 0.4 mg and doxorubicin 9 mg/m² over 24 hours for 4 days with oral dexamethasone 40 mg/d on days 1 through 4). Cycle length was 21 days in each arm. VAD or VMCP was continued for responding patients until the myeloma protein concentration after two successive courses of therapy reached a “plateau,” which was defined as no change in myeloma protein concentration after two successive courses of therapy. Patients refractory to their allocated arm of initial chemotherapy were crossed over to the other arm. Patients still refractory after this crossover procedure received high-dose melphalan (140 mg/m², by 1-hour perfusion) if aged under 55 years.

After this initial chemotherapy, the responding and refractory patients were considered eligible for ABMT. We excluded patients with bad performance status (2 or more, World Health Organization [WHO] scale); (2) granulocyte count < 5000/mm³; (3) platelet count < 75,000/mm³. IFN α was administered subcutaneously three times a week in a dose of 3 x 10⁶ U/m² of body surface area. IFN α was maintained until relapse.

Response criteria. The following definitions were applied both for standard dose chemotherapy before ABMT and for high-dose therapy. Complete remission (CR), absence of monoclonal gammapathy on electrophoresis analysis of both serum and urine and 5% or fewer plasma cells of normal morphology on bone marrow aspirate; partial response (PR), 50% decrease in serum paraprotein and/or 90% decrease in Bence Jones protein; progression, reappearance of detectable paraprotein and/or recurrence of bone marrow infiltration for patients in CR, 50% increase in measurable paraprotein above “plateau” on two samples 4 weeks apart for patients in PR.

Statistical analysis. The proportions of patients with a given characteristic were compared by chi-square test or Fisher’s exact test. Differences in the means of continuous measurements were tested with Student’s t-test controlled by nonparametric Mann-Whitney U-test. All tests were two-sided. Relapse-free survival and survival curves were plotted according to the method of Kaplan-Meier and compared by the log-rank test. Prognostic factors for relapse after ABMT were determined by the Cox proportional hazard model for covariate analysis. The following variables were included in the univariate analysis: sex, age, pretreatment β2 microglobulin, Ig isotype, VAD versus VMCP as initial chemotherapy, response to initial chemotherapy, bone marrow graft plasmacytosis, and CR versus PR after ABMT.

RESULTS

Initial randomization. Sixteen patients were randomly assigned to VAD and 19 to VMCP as initial chemotherapy. As shown in Table 1, patient characteristics of each group were similar, and no significant differences were found with regard to sex, age, stage, Ig isotype, or pretreatment β2 microglobulin level.

Initial chemotherapy. In the VAD group, 8 of 16 patients (50%) reached PR after VAD. The eight nonresponding patients were crossed over to VMCP, of which only one patient responded. Four patients (ages under 55 years; see Materials and Methods) refractory to both VAD and VMCP received HDM, and all of them achieved PR. Finally, 13 patients (81%) reached PR after initial chemotherapy and 15 patients (93%) received ABMT. One patient with progressive disease was excluded for renal failure. The mean interval between diagnosis and ABMT was 8.8 months (SD = 3).

In the VMCP group, 12 patients (63%) reached PR after VMCP. The seven nonresponding patients were crossed over to VAD, of which only one patient responded. Two
patients (aged under 55 years; see Materials and Methods) refractory to both VMCP and VAD received HDM, and one of them achieved PR. Finally, 14 patients (74%) reached PR after initial chemotherapy and 16 patients (84%) received ABMT. Three patients were excluded for the following reasons: one patient with progressive disease for performance status = 3; one patient with PR for insufficient bone marrow collection; and one patient with progressive disease undergoing allogeneic bone marrow transplantation. The mean interval between diagnosis and ABMT was 8.5 months (SD = 3.4).

As shown in Table 2, the overall response rate after initial chemotherapy was 27 of 35 (77%), and 31 patients (89%) could receive ABMT. No significant difference was found between VAD and VMCP with regard to response rate, inclusion for ABMT, and interval between diagnosis and ABMT.

ABMT. Thirty-one patients (89%) received ABMT. The mean interval between diagnosis and ABMT was 8.7 months (SD = 3.2). Bone marrow graft contained 2 to 3.8 x 10^9 nucleated cells per kilogram of body weight (median = 2.7). The graft was unpurged and the median plasma cell contamination was 6% (range 1 to 38). The major toxicity of ABMT was myelosuppression. The mean number of days with neutropenia (≤500/mm^3) was 17 (range 10 to 80). The median number of days with thrombocytopenia (≤25,000/mm^3) was 19 (range 11 to 130). During neutropenia the median number of days with fever (≥38°C) was 5 (range 2 to 23). Two patients developed pneumonia (one staphylococcus, one aspergillus) and four patients developed septicemia (three streptococcus, one Pseudomonas). One patient, initially treated with VAD, VMCP, and HDM, died on day 35 of hepatic veno-occlusive disease.

IFN α therapy after ABMT. Thirty patients received IFN α as maintenance therapy after ABMT. IFN α was introduced between 1 and 7.7 months after ABMT (median = 2.6). The mean neutrophil count at the start of IFN was 1,930/mm^3 (range 500 to 5,994). This value remained stable after 1 month of IFN therapy (mean: 1,534/mm^3; range 500 to 7,320). Treatment was not interrupted for neutropenia. The mean platelet count at the start of IFN was 118,000/mm^3 (range 70,000 to 230,000). A significant decrease (P < .001) was observed after 1 month of therapy (mean = 75,000/mm^3; range 16,000 to 175,000). IFN therapy was transiently interrupted in three patients (for 1, 3, and 3 months) because of thrombocytopenia under 50,000/ mm^3 (36,000/mm^3, 32,000/mm^3, and 16,000/mm^3). Patients received IFN for 0.5 to 30.5 months (median = 11.7). All progression-free patients are still being treated without dose reduction.

Overall response rate. After initial chemotherapy, no patients were in CR and 27 of 35 (77%) were in PR. After ABMT, 15 of 35 (43%) reached CR, and 14 of 35 (40%) remained in PR with a 90% decrease in measurable paraprotein among six of them. (We used 35 as denominator on an intention-to-treat basis.) The time to reach CR after ABMT ranged from 1.2 to 10.3 months (median = 4.2). Fourteen of the 15 patients reaching CR did so after the initiation of IFN therapy. Six initially resistant patients received HDM before HDM/TBI: four patients achieved CR after ABMT, one patient died of hepatic veno-occlusive disease during ABMT, and one patient was excluded and received allogeneic BMT. Different prognostic variables to reach CR were tested for patients with an evaluable response after ABMT (Table 3). Pretreatment β2 microglobulin level was the only prognostically important variable. Indeed, the β2 microglobulin level at diagnosis was lower (P < .01) for patients achieving CR (mean = 3.1; SD = 1.5) than for patients who did not (mean = 5.9; SD = 3.1).

Progression after ABMT. Patients have now been observed for 3 to 33 months after ABMT (median = 15.5). During follow-up, 22 patients have remained progression-free and eight patients have progressed (one from CR, six from PR, and one from stable disease). The 33-month, post-ABMT probability of progression-free survival was 53% (95% confidence interval = 30.2 to 77.6). Table 4 summarizes the variables tested as prognostic factors for duration of response. In univariate analysis, graft plasmacytosis and the absence of CR after ABMT were the only parameters significantly associated with a shorter progression-free survival. However, in the multivariate analysis, the only variable that entered the regression model at a significant level was the absence of CR after ABMT. Thus, the 33-month, post-ABMT probability of progression-free survival was 85% (95% confidence interval = 40 to 100) for patients achieving CR after ABMT versus 24% (95% confidence interval = 0 to 50) for patients not achieving CR after ABMT.

Table 2. Results of Initial Chemotherapy

<table>
<thead>
<tr>
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<th>VAD (n = 16)</th>
<th>VMCP (n = 19)</th>
<th>Total (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial partial response (%)</td>
<td>8 (50)</td>
<td>12 (63)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Partial response after crossover/ no. of patients crossed over</td>
<td>1/8</td>
<td>1/7</td>
<td>2/15</td>
</tr>
<tr>
<td>Partial response after HD/ no. of patients treated with HD</td>
<td>4/4</td>
<td>1/2</td>
<td>5/6</td>
</tr>
<tr>
<td>Overall pre-ABMT response (%)</td>
<td>13 (81)</td>
<td>14 (74)</td>
<td>27 (77)</td>
</tr>
<tr>
<td>No. of patients treated with ABMT (%)</td>
<td>15 (93)</td>
<td>16 (84)</td>
<td>31 (89)</td>
</tr>
<tr>
<td>Mean interval between diagnosis and ABMT in months (SD)</td>
<td>8.8 (3)</td>
<td>8.5 (3.4)</td>
<td>8.7 (3.2)</td>
</tr>
</tbody>
</table>

None of the results differed significantly between treatment groups.
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Table 4. Prognostic Factors for Duration of Response After ABMT

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>.45</td>
</tr>
<tr>
<td>M-Protein (IgG/IgA + BJ)</td>
<td>.9</td>
</tr>
<tr>
<td>Pretreatment (β2 microglobulin)</td>
<td>.9</td>
</tr>
<tr>
<td>Initial treatment (VAD/VMCP)</td>
<td>.07</td>
</tr>
<tr>
<td>Pre-ABMT response (PR/refractory)</td>
<td>.9</td>
</tr>
<tr>
<td>Graft plasmacytosis</td>
<td>.05</td>
</tr>
<tr>
<td>Response after ABMT (CR/PR)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Graft plasmacytosis</td>
<td>.3</td>
</tr>
<tr>
<td>Response after ABMT (CR/PR)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Confidence interval = 4.5 to 64) for patients who did not (P < .03) (Fig 1).

Salvage therapy for relapse after ABMT. During follow-up, eight patients have progressed. Two patients are not yet treated. Two patients received VAD: one of them responded and is still alive 14 months after relapse, the other patient did not respond and died with progressive disease. Four patients received HDM (140 mg/m², supported with recombinant human granulocyte-macrophage colony-stimulating factor, without bone marrow rescue); three of them achieved complete response and one achieved partial response.

Survival. Patients have now been observed for 9 to 42 months after diagnosis (median = 24). During follow-up, five patients died for the following reasons: four patients because of progressive disease (including three patients who did not receive ABMT) and one patient because of hepatic veno-occlusive disease after ABMT. The 42-month, post-diagnosis probability of survival was 81% (95% confidence interval: 58 to 94) for the 35 patients included in this trial (Fig 2).

Discussion

Our study demonstrates the feasibility of a three-phase strategy incorporating IC, high-dose therapy, and IFN α maintenance therapy for previously untreated patients. Indeed, 31 of 35 patients were able to receive ABMT after initial chemotherapy, and in only 1 of 35 did toxic death occur. It proved possible to start IFN α early after ABMT (median = 2.6 months), and during a median period of treatment of 11.7 months only three transient interruptions were necessary because of thrombocytopenia. Furthermore, this strategy was shown to be applicable to patients up to 65 years. Because the median age of multiple myeloma is about 60 years, such a combined therapy appears suitable in a large number of patients.

In this study, initial conventional chemotherapy was aimed to decrease the tumor mass, decrease the bone marrow graft infiltration, and improve performance status and renal function before ABMT. Several investigators have proposed the VAD regimen in this setting. VAD, as first-line therapy, has been reported to induce a rapid and high response rate. It has also been suggested that VAD preferentially reduces more differentiated tumor cells, whereas melphalan, included in the conditioning regimen of ABMT, was more effective against myeloma precursors. Therefore, successive use of these two treatments that lack cross-resistance and affect different tumor cells was expected to induce a short interval between diagnosis and ABMT, a high response rate, and a long duration of response after ABMT. However, in our trial the interval between diagnosis and ABMT, the response rate, and progression after ABMT were not significantly different between patients initially treated with VAD or VMCP. Thus, larger trials designed to answer this question are warranted to give definitive conclusions.

We report here an overall response rate of 83%, with 43% of patients achieving CR. According to previous studies based on conventional chemotherapy, such an incidence of response appears to be due to the introduction
of high-dose therapy in our three-phase treatment. Patients were prepared for ABMT with the combination of TBI and HDM. This melphalan-TBI conditioning regimen has been shown to improve the response rate induced by melphalan alone in refractory patients.\textsuperscript{14,17} However, Gore et al\textsuperscript{13} recently reported a similar 50% rate of CR (using the same response criteria) with HDM alone as consolidation of first-line therapy. Therefore, the role of added TBI to increase HDM response rate remains to be answered in the early phase of the disease. Pretreatment prognostic variables to reach CR have been analyzed in patients with an evaluable response after ABMT. No differences were found between patients who reached CR and those who did not, with regard to age, M-protein, graft plasmacytosis, and pre-ABMT response. Thus, our results confirm those reported by Jagannath et al,\textsuperscript{22} who showed that patients with primary unresponsive disease may have a favorable outcome after ABMT. In our study, the only pretreatment variable found to affect the probability of achieving CR was β2 microglobulin value. β2 microglobulin level at diagnosis was lower for patients achieving CR than for patients who did not (P < .01). β2 Microglobulin is also the most important prognostic factor of response and survival after conventional chemotherapy.\textsuperscript{23,24} Thus, high-dose therapy does not modify the prognostic value of this marker. Furthermore, this suggests that patients with low β2 microglobulin may preferentially benefit from high-dose therapy because they achieved a high rate of CR and a sustained duration of response. Thus, future prospective trial testing the effect of high-dose therapy should not be restricted to patients with high β2 microglobulin level.

An important aim of this study was to evaluate the impact of the combined therapy on remission duration. Our study showed a 33-month post-ABMT probability of progression-free survival of 53% (95% confidence interval 30.2 to 77.6), with a median follow-up of 24 months after diagnosis and 15.5 months after ABMT. We consider these results as promising because our study was targeted to severe myeloma patients with stage III DS, 71% of whom had pretreatment β2 microglobulin levels above 4 mg/L. A recent analysis of prognostic factors in ABMT-treated MM reported that three parameters have an unfavorable impact on the duration of response: resistant relapse at time of ABMT, pre-ABMT high β2 microglobulin value, and non-IgG isotype.\textsuperscript{22} Our study, which included only newly diagnosed MM, found an adverse effect of β2 microglobulin on the nature of response (CR vs PR) but not on the duration of response. We did not find poorer prognosis in IgA and Bence-Jones MM. However, because IgA and Bence-Jones MM have been reported to be more sensitive to IFN therapy than IgG isotype,\textsuperscript{25-28} the use of IFN α after ABMT, in our trial, might be responsible for this discordance. In our nonrandomized study, IFN α was used after ABMT as maintenance treatment. Only one patient achieving CR had relapsed with a median follow-up of 15.5 months after ABMT and 2 years after diagnosis. Although more follow-up is required, these results suggest that the small residual tumor mass of patients achieving CR after ABMT could be highly sensitive to IFN α maintenance treatment.

In MM, there is as yet no consensus regarding a relationship between complete response and more sustained duration of response.\textsuperscript{5} Our study demonstrates such a relationship. Indeed, duration of response was significantly longer for patients achieving CR than for patients who did not (P < .03). Thus, we confirmed results of the Royal Marsden study, using the same CR criteria\textsuperscript{11} based on standard protein electrophoresis and conventional bone marrow aspirate examination. Because such a simple and widely applicable definition of CR is shown to have a prognostic value, we endorse its application to future multicentric trials testing the role of high-dose therapy in MM. Furthermore, such a relationship between CR and duration of response suggests that persistence of monoclonal gammapathy after ABMT is more likely to reflect residual myeloma cells responsible of relapse than more benign and long-lasting preceeding disorders, as it has been speculated.\textsuperscript{5} Finally, these results justify further efforts to decrease residual tumor mass for patients who fail to achieve CR after ABMT. In this regard, repeated use of high-dose therapy should be further investigated.\textsuperscript{29-31}

An important aspect in considering unpurged ABMT in myeloma is the potential detriment of tumor cell infusion. Jagannath et al\textsuperscript{22} previously reported that a greater extent of plasmacytosis in marrow graft was prognostically unimportant. In our trial, response rate was not significantly affected by graft plasmacytosis, even if the mean graft plasmacytosis appeared lower for patients achieving CR than for patients who did not (respectively: 5.7%, SD = 4.4 vs 12.1%, SD = 12.3, P < .1). Furthermore, duration of response was not related to graft plasmacytosis in multivariate analysis even if such a relation was found in univariate analysis. Thus, in our study no significant relation could be
found between bone marrow plasmacytosis and response or duration of response. However, larger trials that analyze not only plasma cell percentage but also plasma cell labeling index in the graft are warranted to give definitive conclusions.

The ultimate aim of treatment in myeloma is clearly to prolong survival, and this is the criterion by which the effectiveness of treatment should be assessed. Our study showed a 41-month, post-diagnosis probability of survival of 81% (95% confidence interval 58 to 94). Compared with previously reported trials based on conventional chemotherapy,12,16 or high-dose therapy,5 this result suggests that a strategy combining intensive treatment to increase response rate and maintenance treatment to prolong duration of response could ultimately improve survival. Furthermore, this strategy appeared applicable to patients up to 65 years. Thus, large number of patients might benefit from this improved survival.

Although promising, these pilot study results need to be confirmed in a prospective randomized trial. A joint European Bone Marrow Transplantation group and European Organization for Research and Treatment of Cancer collaborative study is now underway to compare survival of patients treated with conventional chemotherapy (VMCP/ BVAP regimen) or high-dose therapy (melphalan-TBI regimen supported by unpurged ABMT). IFN α maintenance treatment is being randomized in each arm.

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