High-Dose Chemoradiotherapy and Autologous Blood Stem Cell Transplantation in Multiple Myeloma: Results of a Phase II Trial Involving 63 Patients

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Sixty-three patients with high tumor mass multiple myeloma were treated with high-dose chemotherapy and total body irradiation supported by autologous blood stem cell transplantation. After high-dose therapy, they were monitored for a median of 44 months. Seven patients died early from toxicity. All the other patients, including those whose disease was resistant to previous therapies, showed a tumor mass reduction. At 6 months postengraftment, 40 (71%) of the surviving patients had minimal residual disease and 11 (20%) were in apparent complete remission. During follow-up, 25 out of the 63 (39%) patients relapsed and 16 of these died; 31 (49%) had a sustained remission. The median overall and event-free survival times after transplantation were 59 and 43 months, respectively. The initial serum β2-microglobulin value (> or < 2.8 mg/L) and length of previous therapy (> or < 6 courses of chemotherapy) were the only significant prognostic factors. In all surviving patients, blood stem cell autograft provided satisfactory and sustained haematopoietic reconstitution most often within 15 days. High dose chemoradiotherapy followed by autologous blood stem cell transplantation is thus an important therapeutic option for young patients with aggressive multiple myeloma.

SINCE THE PIONEERING work of McElwain and Powles[1] and Selby et al,[2] who provided evidence that an increase in drug doses resulted in higher remission rates and more marked tumor mass reduction, high-dose therapy has been an important therapeutic option for young patients with multiple myeloma (MM). Several groups have reported preliminary results of trials of high-dose chemotherapy (HDC) administered alone or in combination with total body irradiation (TBI), with allogeneic or autologous bone marrow transplantation (BMT).[3] In a previous study, we showed that blood can be used as the source of hematopoietic stem cells in patients with MM and reported preliminary results of a high-dose treatment supported with autologous blood stem cell transplantation (ABSCT).[4] We now present the results of a phase II trial involving 63 patients treated with HDC, TBI, and ABSCT who have been followed for a median of more than 3.5 years.

PATIENTS AND METHODS

Patients. All the patients with MM from four institutions who were treated between 1986 and 1991 with HDC, TBI, and ABSCT according to the protocol described below were included in this study. Forty-three (68%) were men and 20 (32%) were women. The median age was 44 years (range 29 to 58). The isotype of the monoclonal Ig (MIg) was IgG in 28 cases (44%), IgA in 15 (24%), and kappa or lambda Bence Jones protein in 19 (31%); one patient had a nonsecreting MM. At diagnosis, 52 patients had stage IIIA disease, 4 had stage IIIB, and 7 had stage IIA according to the classification of Salmon and Durie.[5] Nine, 16, and 45 patients initially had hypercalcemia (≥3 mmol/L), anemia (hemoglobin <100 g/L) and major lytic bone lesions, respectively. Serum creatinine levels of the 4 patients with stage IIIB disease were ranged between 280 and 590 μmol/L. The serum β2-microglobulin level (known in 61 patients) was above 6 and 4 mg/L in 12 and 20 cases, respectively, with a median value of 2.8 mg/L (range 1.3 to 10.8; normal upper limit 1.9 mg/L).

Blood stem cell collection was performed at the time of diagnosis in 30 patients while 33 had previously been treated. The latter had received 1 to 20 (median 6) monthly courses of various regimens containing alkylating agents (including melphalan in 9 patients), vincristine, steroids, and/or doxorubicin. In addition to chemotherapy, 16 patients had been focally irradiated on threatening or painful lesions at doses allowing subsequent TBI.

Blood stem cell collection. Blood stem cell collection was performed after administration of a semi-intensive chemotherapy regimen combining cyclophosphamide (1,500 mg/m^2), doxorubicin (90 mg/m^2), vincristine (1.4 mg/m^2), and steroids. This treatment led to a short period of cytopenia and peripheral blood mononuclear cells were collected at hematologic recovery by three to five leukapheresis procedures performed on consecutive days, as previously described.[4] Harvested cells were analyzed for their content of granulocyte-macrophage progenitor cells using single-layer agar culture systems to grow granulocyte-macrophage colony-forming-units (CFU-GM).[6] An adequate number of CFU-GM (varying from one center to the next according to the used cell culture conditions) was collected after one course of chemotherapy in 55 patients and after two or more in 8 patients.

The median time from blood stem cell collection to ABSCT was 3.8 months. During this period, patients received monthly courses of either a conventional dose therapeutic regimen (usually combining steroids, vincristine, cyclophosphamide, and, during the first two cycles, doxorubicin) or a VAD-like regimen (combining continuous 24-hour infusion of vincristine [0.4 mg/d] and doxorubicin [9 mg/m^2/d] delivered for 4 days and intravenous methylprednisolone [0.4 g/d]).

HDC, irradiation, and graft. HDC protocol consisted of carmustine (120 mg/m^2 orally at day −8, etoposide (250 mg/m^2 intravenously at day −8 to −6), and melphalan (140 mg/m^2 given as a single 2 hours perfusion at day −4); cyclophosphamide (60 mg/kg given as a short perfusion at day −5) was added to this regimen in the last 26 patients.

TBI was delivered either in a single dose of 10 Gy during a 6-hour

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period (31 patients) at day −1 or in 6 fractions of 2 Gy at day −3 to −1 (32 patients). Lung irradiation was reduced to 8 and 10 Gy, respectively.

Cryopreserved autologous peripheral blood mononuclear cells were reinfused at day 0.

HDC, TBI, and ABSCT were performed in a protected unit. Patients received partial digestive decontamination. Supportive care was given when needed and included blood products and broad-spectrum antibiotics. All patients were advised of the inherent risks of high dose therapy and gave their informed consent.

Follow-up. Since 1989, patients have been considered for treatment with recombinant α-interferon (IFN) after the graft. IFN therapy was started 6 to 12 months after high-dose therapy, according to the patient's condition and hematologic status. IFN was administered subcutaneously three times a week at 3 to 5×10^6 U. Twenty-three patients received the drug for a median of 6 months (range 1 to 36 months). The others did not receive treatment unless relapse occurred.

Patients who relapsed were given conventional or VAD-like regimens, sometimes in combination with focal irradiation. Five patients received a second course of high-dose therapy (busulphan 16 mg/kg and cyclophosphamide 120 mg/kg or melphalan 140 mg/m^2) supported with either allogeneic (3 cases) or autologous (2 cases) stem cell transplantations.

Response criteria. Disease response was defined as follows. (1) Complete remission (CR): 5% or fewer plasma cells of normal morphology on bone marrow smears (performed 1 and 6 months after ABSCT and, thereafter, at least once a year) and absence of MIg by immunochemical analysis (immunoelectrophoresis and immunofixation) of serum and of a 100-fold concentrated urine sample. (2) Minimal residual disease (MRD): 5% or fewer plasma cells on bone marrow smears associated with a decrease in the MIg level of at least 90%. (3) Partial response (PR): 50% decrease in serum MIg and/or 75% decrease in Bence Jones protein levels. Refractory disease was considered in the absence of a decrease in serum MIg and Bence Jones protein levels of at least 50% and 75%, respectively. Progressive disease and relapse were defined by the reappearance of the MIg, a 25% increase in its level, or by the occurrence of a plasma cell tumor.

Statistical analysis. Statistical analysis was based on January 1, 1993 as the reference date. Overall survival and event-free survival (ie, time to occurrence of either relapse or death) were estimated from the date of beginning of HDC by the Kaplan-Meier method. The predictive value of baseline parameters was tested by the log rank test for both endpoints. Two-sided tests were performed with $\alpha = 5\%$. Statistical analysis was performed using the statistical analysis system (SAS) package.

RESULTS

Response to high-dose chemoradiotherapy and ABSCT. Before high-dose therapy and transplantation, the 63 patients had received 3 to 27 (median 5) courses of chemotherapy delivered in a median of 9 months (range 3 to 90); 16 also received a focal irradiation. At the time of HDC, TBI, and ABSCT, no patients were in CR, 19 (30%) were in PR, and 37 and 7 had refractory or progressive disease, respectively. All had a serum creatinine level under 300 μmol/L.

Seven patients (11%) died during the transplantation procedure or shortly after because of interstitial pneumonia (3 cases), hepatic veno-occlusive disease, viral hepatitis, brain hemorrhage, or fungal infection (one case each). Six months after high-dose therapy, the 56 surviving patients were in remission, 16 (28.6%) in PR, 11 (19.6%) in CR, and 29 (51.7%) with a MRD. Among the latter, 7 had all criteria for CR but monoclonal light chains were detected in a 100-fold-concentrated urine sample. Patients who were in CR or MRD accounted for 71% of the survivors and 63% of the overall group.

Serum levels of polyclonal Ig increased after HDC and TBI to reach nearly normal values in two thirds of the patients. During follow-up, no obvious radiologic evidence of bone healing was seen in any of the 55 patients who initially had bone lesions but an increase in spine bone mass density, as measured by dual x-ray absorptiometry, was observed in 8 of 10 assessed patients.[7]

Survival and disease-free survival. At the reference date of January 1, 1993, the median follow-up after ABSCT was 44 months (range 16 to 74).

Overall and event-free survival is shown in Fig 1. During follow-up, 31 patients had a sustained remission, including 22 in CR or MRD; 23 were followed for more than 36 months. Twenty-five patients relapsed 7 to 50 months post-engraftment. Of these, 8 were in PR, 4 in CR, and 13 with MRD after high-dose therapy. Sixteen patients died from progressive disease (14 cases) or complications of salvage therapy (2 patients, both during second high-dose treatment).

Overall, 23 patients died, 7 at the time of the ABSCT or shortly after and 16 during relapse, 8 to 59 months post-engraftment. Survival rates were 86%, 79%, and 69% after 1, 2, and 3 years (standard deviation: 4%, 5%, and 6%). The median survival time was 59 months (Fig 1). Thirty-seven patients were alive more than 3 years after HDC, TBI, and ABSCT. Taking into account all deaths and relapses, a total

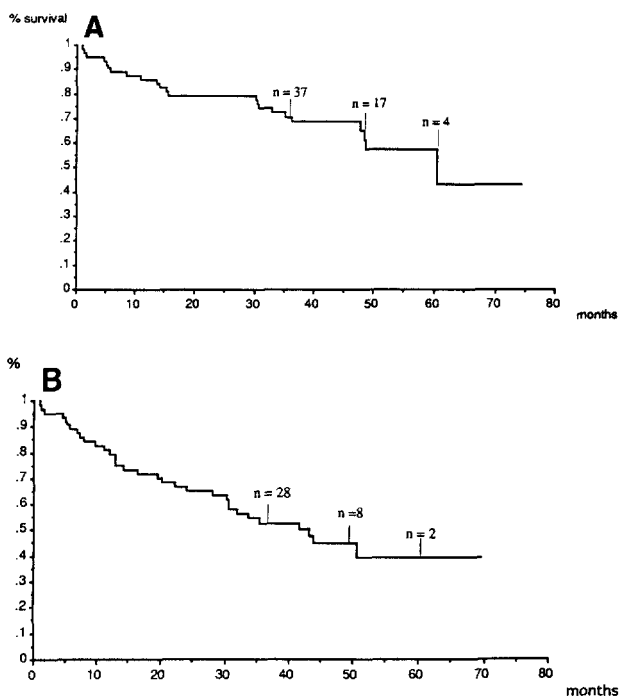

Fig 1. (A) Overall survival from ABSCT. (B) Event-free interval from ABSCT.

of 33 events occurred and the median event-free survival was 43 months (Fig 1).

Prognostic factors. Several parameters were evaluated for predictive and prognostic value for response to high-dose therapy and patient's outcome (Table 1). CR and MRD were more frequent in patients who were in PR before the graft (17 out of 19) than in those whose disease was unresponsive to pretransplantation treatment (23 out of 44). No other factor was predictive of postgraft disease status. Interestingly, there were 6 CR among the 22 patients treated with the HDC regimen including cyclophosphamide compared with 5 of the 34 who did not receive cyclophosphamide.

There was no significant advantage in terms of event-free and overall survival for patients with IgG MM. In contrast, 3-year survival was 84% in patients whose serum β2-microglobulin level at diagnosis was below 2.8 mg/L compared with 53% in the others ($P = .002$; log rank test); median overall and event-free survival are not yet reached for the former compared with 47 and 20 months for the latter (Fig 2 and Table 1). The status of the disease immediately before transplantation had no prognostic value, whereas the duration of previous therapy was a significant predictive factor for outcome; survival was indeed significantly better in patients whose pre-engraftment therapy included a total number of courses of chemotherapy of 6 or less ($P = .04$) (Table 1).

Table 1. Prognostic Factors for Overall and Event-Free Survival

	Patients (n = 63)	Deaths (n = 23)	P	Events* (n = 33)	P
Age (yr)					
<45	32	9	.07	17	.66
>45	31	14		16	
β2m (mg/L)†					
<2.8	32	6	.002	11	.0007
>2.8	29	16		21	
MIG					
IgG	28	9	.76	12	.24
other	35	14		21	
Chemotherapy before HDC-TBI and ABSCT Duration (mo)					
<5	34	9	.01	15	.008
>5	29	14		18	
No. of courses					
<6	46	15	.04	23	.08
>6	17	8		10	
Pretransplantation status					
PR					
yes	19	6	.39	9	.47
no	44	17		24	
High-dose chemotherapy					
With CPM‡	26	5	.20	9	.15
Without CPM	37	18		24	
Post-transplantation status§					
PR	16	6	.32	8	.64
MRD	29	8		14	
CR	11	2		4	

* Either death or relapse.

† Serum β2 microglobulin level at diagnosis (two missing values).

‡ Cyclophosphamide.

§ Six months postgraft, in the 56 surviving patients.

Addition of cyclophosphamide to the HDC protocol had no discernible effect on survival. Of note, the response to HDC and TBI was not predictive of the outcome: the length of survival was similar in patients who were in CR after the transplantation and in those who achieved PR or MRD ($P = .32$). To search for a deleterious effect of the reinfusion of eventual tumor cells contaminating the graft, patients who were engrafted with a small number of peripheral blood mononuclear cells (less than 3×10^8/kg body weight) were compared with those who received a higher number: there was no difference between the two groups. The impact of IFN therapy on outcome could not be evaluated because IFN was administered to selected patients; interestingly, 6 out of the 8 patients in sustained remission 4 years after high-dose therapy have never received IFN.

Hematologic recovery and toxicity. For the 56 surviving patients, the period of aplasia was relatively short: leucocyte and granulocyte counts reached 10^9/L and 0.5×10^9/L within a median time of 13 and 15 days (range 9 to 45) and the median time required for the recovery of platelets to 25×10^9/L and 50×10^9/L was 16 (range 9 to 150) and 30 (range 10 to 370) days, respectively. Hemoglobin recovery was similarly rapid. During the period of neutropenia, the median number of days with fever (>38°C) was 7 (range 0 to 24). Recovery of granulocytes and platelets was related to the number of reinfused myeloid progenitor cells; no other feature appeared to influence the kinetic of the hematopoietic reconstitution.

ABSCT was followed by satisfactory and sustained hematopoietic reconstitution in all patients but one who was grafted with a borderline number of CFU-GM; he needed transfusions of blood products until the 16th month after high-dose therapy. No late graft failures occurred and the hematologic tolerance of subsequent myelotoxic therapy such as IFN was acceptable. Indeed, IFN was not withdrawn because of cytopenia in any patient. There was no evidence of myelodysplatic disease or frank acute leukemia in any case.

Six patients developed an overt but transient hemolytic and uremic syndrome (featured by anemia with schizocytosis, thrombocytopenia, and renal abnormalities) a few months after transplantation. Most patients in remission had quite a good quality of life and 27 returned to work.

DISCUSSION

We report the results of HDC and TBI followed by ABSCT in 63 patients aged 58 years or less with aggressive MM who were followed for a median of more than 3.5 years. Seven patients died early from toxicity. The others, including those whose disease was resistant to conventional therapy, achieved a marked tumor mass reduction. Six months postengraftment, 71% of surviving patients had MRD or were in CR. During follow-up, 25 patients relapsed, of whom 16 died. The median length of survival after HDC, TBI, and ABSCT reached 5 years and the median event-free survival was 43 months. All patients had

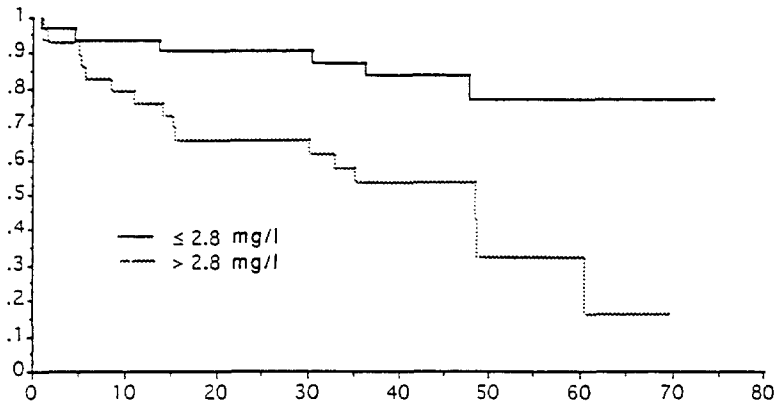

Fig 2. Overall survival from ABSCT according to serum β-2 microglobulin level at diagnosis.

been treated before high-dose therapy and the median overall survival since first treatment was 68 months.

Therefore, these results confirm that high-dose therapy can overcome resistance to conventional therapy and leads to impressive tumor reductions in over 70% of patients with MM. In this series, 11 out of 63 patients (20%) entered CR. CR rates varying from 5% to 50% have been reported by several groups with less intensive protocols, especially high-dose melphalan (HDM) alone or HDM plus TBI.[8-13] These differences are likely explained by more or less stringent criteria used to define CR. For instance, 7 additional patients in the present study would have been considered to be in CR, but for the presence of urinary light chains in 100-fold–concentrated urine samples. Four patients in apparent CR relapsed during follow-up. The detection of residual tumor cells, which can now be achieved using the polymerase chain reaction (PCR),[14] will be of interest to establish the actual rate of CR and the chance of curing such patients.

Overall, few patients achieved CR, despite treatment with a very intensive high-dose therapy protocol. In MM, as in other malignancies, the relationship between dose intensity and CR may not be linear at the highest doses of drugs and radiation and the CR rate may not be improved by more intensive chemoradiotherapeutic regimens. In contrast, the tumor mass at the time of high-dose therapy might be an important factor. Indeed, we observed more frequent apparent CR in patients who had achieved PR before to the high-dose treatment. Accordingly, Gahrton et al,[15] who analyzed the European Registry of patients with MM treated with cyclophosphamide (or alternatives) plus TBI and allogeneic BMT, reported much higher CR rates in patients with stage I disease than in patients with stage II or III disease (78% *v* 36%, respectively).

In the latter study, the duration of response was significantly longer for patients who achieved CR compared with those who did not (48 months for the former). Similar findings were reported by the Royal Marsden Investigators[8] and by Attal et al[13] who treated patients with high tumor mass MM with high-dose therapy and autologous BMT. In contrast, there was no relationship between CR and the duration of remission in our series. Nevertheless, the median relapse-free interval for the 56 patients alive at 6 months, whatever their postengraftment disease status, was 50 months and appeared comparable to that of patients from other series who achieved apparent CR.

The potential role of tumor cells contaminating the hematopoietic graft in the relapses was not analyzed in this study. Previous data have indicated that in most cases no myeloma cells are detectable by conventional Southern analysis of Ig gene rearrangement in B-cell–enriched fractions from leukapheresis performed at blood stem cell collection.[6] Whether this lack or low number of contaminating tumor cells is a true advantage of ABSCT over autologous BMT will be difficult to assess. Future studies should determine, using highly sensitive methods such as allele-specific oligonucleotide PCR,[16] the degree of tumor cell contamination and the possible efficiency of an in vitro purge.

The present study confirms and extends our previous data[4,6] on the capacity of blood transplants to restore satisfactory hematopoiesis in myeloma patients treated with HDC and TBI. In addition, the period preceding hematopoietic recovery was shorter than that observed after BMT.[10,15,17] Another advantage of ABSCT is that it can be used in most patients because adequate peripheral blood stem cells can be collected following chemotherapy in over 90% of untreated MM and in around 70% of previously treated patients.[6] In contrast, allogeneic BMT is possible in no more than 7% of patients with MM[18] and the harvest of autologous bone marrow requires previous cytoreduction even when using an in vitro purging procedure.[19]

With a median follow-up of more than 3.5 years, the median post-high-dose-therapy survival was 5 years in the overall group and much longer in the patients who presented with low serum level of β2-microglobulin or who had not been heavily pretreated. These data compare favorably with those of previous trials based on conventional chemotherapy[20] or high-dose therapy.[3,11-13,15] However, our series included mainly young patients with aggressive disease and randomized trials are required to assess the precise place of high-dose therapy and ABSCT. Finally, the absence of a discernible plateau in the survival curves, especially in patients with high serum β2-microglobulin levels, suggests that cure, if any, might concern only a few patients; other approaches to improve tumor reduction or to lengthen the duration of response remain to be evaluated (such as IFN) or to be developed.

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