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An analysis of which subgroups of multiple myeloma patients, divided according to β_2-microglobulin and plasma cell labeling index, benefit from high dose vs conventional chemotherapy

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ABSTRACT

Background and Objectives. **The clinical advantage of high-dose therapy (HDT) over standard treatment for multiple myeloma (MM) patients has been recently assessed. Which patient subgroups benefit most from this approach is unclear.**

Design and Methods. **To address this issue, the outcome of 54 patients under 55 years old treated with HDT was compared with that of 101 age-matched controls selected from 390 patients who received standard melphalan and prednisone (MP) chemotherapy in a national multi-center trial (M90 protocol).**

Results. **The complete response (CR) rate was 50% in the HDT group compared to 5% in the MP group. Event-free survival (EFS) was three times longer for the HDT patients (median 34.5 vs 12.2 months, $p<0.0001$), though the controls enjoyed a prolonged survival after relapse, and hence there was no statistically significant difference in OS. Overall survival (OS) was analyzed in relation to two major prognostic factors: β_2-microglobulin (β_2-M) and bone marrow plasma cell labeling index (LI). HDT significantly improved OS in poor prognosis patients with a high LI (>1.2%), (median 49.5 vs 32.5 months, $p<0.03$), whereas it did not prolong OS in poor prognosis patients with high β_2-M (> 3 mg/L).**

Interpretation and Conclusions. **In conclusion, HDT has a major impact on CR and EFS, and is the treatment of choice for patients with a high LI. Alternative strategies should be adopted in poor prognosis patients with high β_2-M.**

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Key words: multiple myeloma, autologous transplantation, β_2-microglobulin, labeling index

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Multiple myeloma (MM) is a malignant, uniformly fatal disease of B-cell origin.[1] Since survival has not been improved over the last 30 years by conventional chemotherapy,[2] high-dose therapy (HDT) with autograft has been considered as an alternative approach.[3-5] Its applicability has been widened by the use of peripheral blood progenitor cells (PBPC) and hemopoietic growth factor support to drastically reduce the period of absolute pancytopenia and transplant-related mortality.[6,7] However, in spite of reported complete response (CR) rates of 30-50%, relapse remains the rule.[8,9]

HDT improved response rate, event-free survival and overall survival compared with conventional therapy in a French randomized trial with bone marrow (BM) autograft[10] and in a large case-matched historical control with PBPC support.[11] The efficacy of an intensified chemotherapy approach (melphalan 100 mg/m^2) followed by PBPC support has also been assessed in elderly MM patients (median age 63 years). The outcome of the patients treated with the intensified approach was compared with that of patients matched for age and β_2-microglobulin (β_2-M) level treated with the conventional melphalan and prednisone regimen.[12] However, prolonged survival has also been reported in a group of responding MM patients potentially candidates for HDT but managed with conventional chemotherapy.[13] Conflicting results about patient outcome may be explained by the well-known heterogeneity in terms of response to therapy and survival among MM patients. Indeed, further analyses according to the patients' prognostic characteristics are still required in order to determine the role of HDT in different subgroups of MM patients.

The efficacy of HDT in specific MM patient categories has been assessed in some studies. Patients with primary resistant disease for less than 1 year showed prolonged survival after HDT vs conventional salvage therapies.[14] On the other hand, no advantage was seen after primary resistance for more than 1 year.[15] Similarly, high β_2-M, C-reactive protein

(CRP), and abnormal karyotype identified patients with the poorest outcome.[16-18] Finally, HDT conferred a survival benefit in a small series of patients with high bone marrow plasma cell labeling index (LI) compared with a historical control group treated with conventional chemotherapy.[19]

In this study the outcome of 54 patients under the age of 55 treated with HDT was compared with that of 101 age-matched controls from 390 patients who received standard treatment in a national multi-center trial (M90 protocol) during the same period of time.

Design and Methods

High-dose therapy group

Between January 1990 and June 1997, 54 consecutive MM patients received HDT and autologous PBPC support. Patients up to 55 years with Durie and Salmon[20] stage II and III disease qualified for the study. Exclusion criteria included prior treatment, presence of another malignancy, abnormal cardiac function (systolic ejection fraction < 50%), recent (within 3 months) myocardial infarction, abnormal liver function (serum bilirubin > 2.5 mg/dL, or serum aminotransferases fourfold the normal values), abnormal renal function (serum creatinine > 3 mg/dL), diabetes and non-secretory myeloma. Patient characteristics and prognostic factors are illustrated in Table 1. All patients received 2 courses of VAD (vincristine, adriamycin, and dexamethasone) as debulking treatment. Subsequently, PBPC were mobilized and harvested during recovery after cyclophosphamide (CY) given at 7 g/m^2 followed by G-CSF (see below). Apheresis was initiated when the leukocyte concentration recovered to a level of 0.5×10^9/L. A Fresenius AS104 (Germany) blood cell separator was used. Prior to the mobilizing course, further cytoreduction was achieved with three high-dose (hd) sequential schemes: a) etoposide 2 g/m^2 followed 15 days later by methotrexate 8 g/m^2 (14 patients); b) mitoxantrone 30 to 50 mg/m^2 followed 15 days later by etoposide 2 g/m^2 (15 patients); c) CY 5 g/m^2 followed 15 days later by etoposide 2 g/m^2 (25 patients). Details of these schemes have already been reported.[19] The pre-transplant conditioning regimen consisted of melphalan at 140 mg/m^2 and total-body irradiation (10 Gy in 4 fractionated doses) for patients receiving schemes *a* and *b*; the remaining 25 patients were included in a double-autograft program, consisting of melphalan 200 mg/m^2 for the first transplant and melphalan 180 mg/m^2 plus mitoxantrone 60 mg/m^2 for the second transplant. They then received 5 µg/kg G-CSF until the absolute neutrophil count exceeded 1×10^9/L. No statistically significant difference in terms of response or clinical outcome was observed between the three schemes.

Conventional therapy group

Between January 1990 and December 1994, 390 MM patients were enrolled at diagnosis in the M90 multi-center trial carried out by the *Italian Multiple Myeloma Study Group*. An intensified conventional induction regimen was compared with the standard melphalan and prednisone (MP) regimen. The experimental approach was not statistically superior to the MP one. Thus, 101 patients, treated with MP, and aged less than 55, were selected in the same way as the HDT group (see HDT exclusion criteria) to provide a matched control. The distribution of the main clinical features and prognostic factors was not statistically different between the two groups (Table 1).

Criteria for response

Clinical response was evaluated by serial assessments of bone marrow plasmacytosis and myeloma paraprotein in serum and urine samples, analyzed by standard electrophoresis. Complete response (CR) was defined as disappearance of serum and urine paraprotein detectable by standard electrophoresis and bone marrow plasmacytosis < 5%. Correction of hypercalcemia, anemia, and hypoalbuminemia was also required. Partial response was defined as a >50% reduction of serum myeloma protein, >75% decrease of Bence-Jones proteinuria, without any increase in the size or number of lytic bone lesions. Relapse was defined as an increase of >50% from the lowest level of serum myeloma protein, or an increase in the size or number of lytic bone lesions. Progression was defined as an increase of >25% of the serum paraprotein or an increase in the size or number of lytic bone lesions during the induction treatment.

Statistical analysis

The proportions of patients with a given characteristic were compared by the chi-square test. Event-free survival duration was calculated from the beginning of treatment until the occurrence of an event or the date at which the patient was last known to be in remission. The following events were considered: toxic death or any toxicity that would prevent treatment completion, death from any other causes, disease

Table 1. Patient characteristics.

	MP	*hd-therapy*	*p value*
No. of patients	101	54	
Age > 50 yrs	51	48	ns
Creatinine >3 mg/dL	12	8	ns
Stage II	31	28	ns
Stage III	68	72	ns
IgG	67	60	ns
IgA	31	28	ns
Light chain	12	12	ns
B_2M > 3 mg/L	46	49	ns
LI > 1.2%	30	35	ns

MP = melphalan and prednisone; hd-therapy = high-dose chemotherapy.

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Table 2. Response to therapy.

	MP %	*hd-therapy* %	*p value*
Complete response	5	50	
Partial response	45	40	
No response	50	10	0.0001

progression, relapse. Overall survival duration was measured from the date of diagnosis to date of death or last follow-up evaluation; a survival duration starting from event to death or last follow-up evaluation was also calculated. The actuarial durations of survival were plotted as curves according to Kaplan and Meier.[21] Differences between the curves were evaluated by the log-rank method. Survival was also examined by stratifying patients according to their LI and serum β_2-M levels. All data were processed with the SAS statistical software package (SAS Institute Inc, Cary, NC, USA).

Results

Treatment feasibility and response

Of the 54 patients in the HDT group, 11 did not proceed to transplantation because of treatment-related toxicity (4 patients), disease progression (4 patients) or inadequate PBPC collection (3 patients); patients with disease progression also had poor PBPC mobilization. Toxicities included: severe fungal infection (2 patients) and impaired renal function (2 patients: 1 occurring after mitoxantrone treatment, 1 after high-dose etoposide). No treatment-related mortality was observed within 12 months. Of the 101 patients of the control group, 4 early deaths (within 3 months from diagnosis) occurred: 2 related to infection, and 2 to disease progression.

Response to treatment is shown in Table 2. A significantly higher CR rate was documented in the HDT group, whereas the proportion of patients with no response or disease progression was significantly higher in the controls. In a multivariate analysis the only factor significantly associated with low response rate was high β_2-M level ($p<0.05$).

Long-term outcome

After a median of 57 months (range 13-78) of follow-up, 24 HDT patients have died (44%). Sixteen are still in first remission, the other 14 have received salvage regimens. In the control group, after a median of 76 months (range 12.5-78) of follow-up, 56 patients have died (55%), and 45 patients are still alive. Nine are still in first remission, the other 36 (80%) have received salvage regimens. One patient received an allograft transplant during remission phase, and 3 an autologous transplant at relapse. These patients were censored at the time of transplantation.

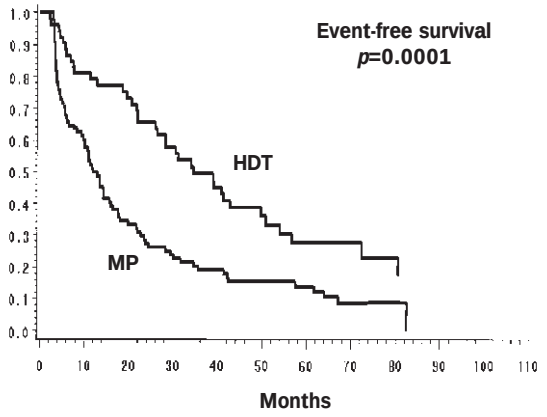

Figure 1. Event-free survival of 54 patients treated with high-dose therapy (HDT), and 101 patients treated with conventional melphalan and prednisone chemotherapy (MP).

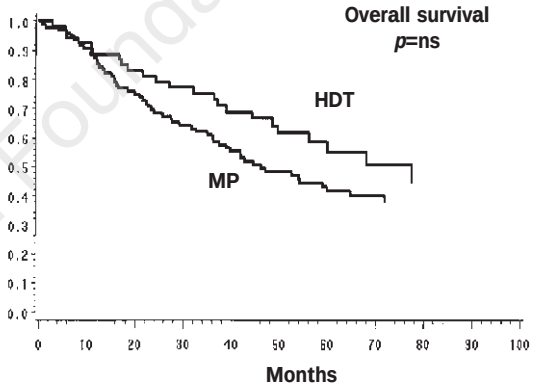

Figure 2. Overall survival of 54 patients treated with high-dose therapy (HDT), and 101 patients treated with conventional melphalan and prednisone chemotherapy (MP).

Median event-free survival (Figure 1) was 34.5 months after HDT and 12.2 months after conventional chemotherapy ($p<0.0001$). Median survival from event to death was 18.1 months after HDT and 28.8 months after standard treatment ($p<0.04$). The overall survival curves (Figure 2) of patients treated with HDT versus conventional chemotherapy were not statistically significantly different.

Overall survival was also evaluated according to serum β_2-M level and bone marrow plasma cell LI. Median overall survival was similar ($p = 0.36$) in poor prognosis patients (β_2-M > 3 mg/L) treated with either HDT or conventional therapy (Figure 3). Median overall survival was also similar in good prognosis patients (β_2-M < 3 mg/L) treated with either ther-

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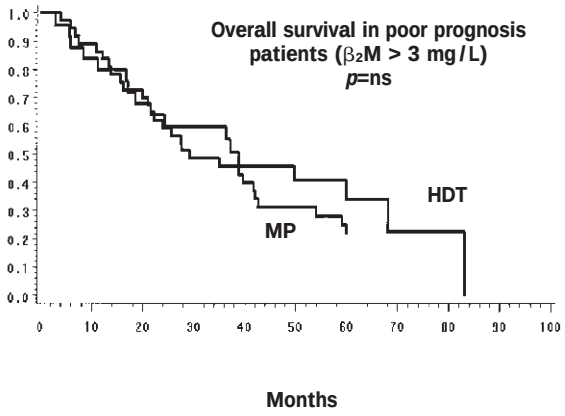

Figure 3. Overall survival of poor prognosis patients (β_2-M > 3 mg/L) treated with high-dose therapy (HDT), and conventional melphalan and prednisone chemotherapy (MP).

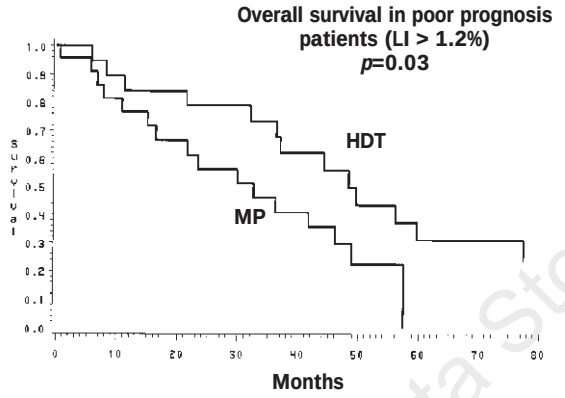

Figure 4. Overall survival of poor prognosis patients (LI > 1.2%) treated with high-dose therapy (HDT), and conventional melphalan and prednisone chemotherapy (MP).

apy (median 71.7 vs 68 months). Poor prognosis patients with high LI treated with HDT had a significantly longer overall survival (49.5 vs 32.5 months, $p = 0.03$) (Figure 4). However, overall survival was not influenced by the type of treatment in good prognosis patients with low LI (median 61 vs 54 months). Within the HDT group the prognostic significance of LI was lost: survival was similar in patients with high or low LI (median 49.5 vs 61 months).

Discussion

This study shows that HDT offers major advantages in the management of MM patients at disease onset in terms of CR rate and event-free survival in comparison with similar patients treated with conventional chemotherapy. When patients were stratified according to main prognostic features, the treatment approach had no influence on the outcome of high-β_2-M patients. By contrast, HDT significantly improved the overall survival of patients with high plasma cell LI.

A total of 54 patients were consecutively enrolled between 1990 and 1997 in protocols based on autograft with PBPC collected after hd-CY and growth factor. To achieve the highest tumor reduction prior to autograft,[22] a debulking phase was included with three schemes; the ongoing program also includes a double autograft. Despite variability in the delivery of hd-drugs, no major difference in treatment outcome was found. Furthermore, all patients had similar clinical characteristics, including age less than 55, absence of any previous cytotoxic treatment and diagnosis of overt MM. Thus, our study group was sufficiently homogeneous to evaluate the impact of a HDT as part of front line treatment of MM.

A control group was obtained from a randomized multi-center study evaluating a chemotherapy program at conventional dose. From among 390 enrolled patients, 101 age-matched patients with clinical characteristics comparable to those of the patients enrolled in the HDT were chosen. Although randomization between different therapies is the best strategy to define their advantages, in our study the control group was not a historical one, since the multi-center study was carried out simultaneously with the hd-program. Overall survival of conventionally treated patients was significantly prolonged compared with previous studies in recent trials. This has been attributed to improved support therapies and salvage regimens.[23] Hence, we feel that our control group was very appropriate, since it reflects the current results offered by conventional treatment. Several national committees recognize the superiority of HDT versus conventional chemotherapy, and HDT is now considered an appropriate practice for MM at presentation;[24] thus, the accrual of young MM is hampered in randomized trials.

Compared to controls, patients enrolled in the HDT trial displayed a significantly increased CR rate (5% vs 50%), and event-free survival. This is in line with results of the French randomized trial.[10] Similar results were reported by Barlogie *et al.*[11] in a study comparing the outcome of patients receiving a double autotransplant with that of historical controls receiving standard therapy according to SWOG trials. The higher tumor reduction and the prolonged event-free survival offered by the HDT regimen are of clinical relevance. CR allows an excellent performance status and a better quality of life than partial remission. Furthermore, prolonged event-free survival implies fewer chemotherapy courses delivered than for patients who are managed with conventional chemotherapy. Finally, the cost of life gained with transplant compares favorably with that achieved with conventional chemotherapy, as already report-

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ed.[25] All these considerations support the preferential use of HDT in the management of MM at disease onset.

Both the French study and that by Barlogie *et al.* showed a significantly prolonged overall survival with HDT.[4,10] This was not confirmed in our analysis, but this may simply be a consequence of the smaller number of patients in our study. It is clear, however, that a discrepancy does exist between the very high statistical significance for event-free survival, and the lower one for overall survival in all these studies. We observed that survival from first event to death was prolonged among patients receiving conventional chemotherapy as opposed to HDT. This observation stresses the importance of evaluating new approaches that allow HDT to be scheduled at both induction and recurrence. A second autograft, in fact, could not be performed because most patients were unable to produce adequate quantities of PBPC at relapse. Therefore, repeated PBPC collections might be performed at diagnosis in order to have enough material to make HDT affordable later.

Some prognostic factors known to predict the outcome of conventionally-treated patients have an impact on the survival of patients treated with high dose regimens. Low CRP and β_2-M levels, non-IgA isotype, normal cytogenetics, and high-dose therapy performed within 12 months from diagnosis are independent favorable transplant variables.[16] The strong prognostic value of β_2-M level was confirmed in our study. Indeed, a very poor outcome was observed in patients with high β_2-M, regardless of whether treated conventionally or with the high-dose protocol. In this subgroup of patients, the choice of chemotherapy has very little, if any, influence on the natural history of the disease. Thus other strategies, including allogeneic transplantation, should be investigated at least for younger patients presenting with high levels of β_2-M.

Plasma cell LI defines the proliferative state of the neoplastic clone, and is a well-known prognostic variable independent from β_2-M.[26,27] A poor outcome has been reported in the past for patients with high LI.[26,28] Here we show that HDT changes the outcome of these patients. In patients presenting with LI >1.2 the HDT consented a significantly longer overall survival than that in patients receiving conventional therapy. The improved survival in these patients abolishes the difference from patients with low LI. Hence, LI is no longer an adverse prognostic factor if patients are treated with HDT.

The favorable outcome of patients with a high LI following HDT also has a biological rationale. A high proliferative state often implies marked chemosensitivity along with a better clinical response to intensive cytoreduction. A HDT analogous to ours has been successfully employed in diffuse large cell lymphomas, a tumor with high proliferative activity.[29] One can speculate that MM with a high LI may behave the same way, thus representing a separate entity distinct from the more indolent and more chemoresistant low-LI MM.

In conclusion, our results strongly suggest the superiority of HDT for patients below 55, at least in terms of CR and event-free survival. However, additional efforts should be made to identify other subsets of patients who would be good candidates for HDT.

Contributions and Acknowledgments

MB designed the study, was responsible for data management and prepared the manuscript, CT, MG and AP participated to the study design and collaborated to prepare the manuscript, CA performed the data analysis and contributed to the interpretation of the data, ST, AD, VC, VML, SM, PM and FM collaborated in patient care and data analysis, AP participated in the study design and gave his final approval to the manuscript.

The criteria for the order in which the names of the authors are based on the authors' contribution to the design, analysis and execution of the study, except for MG and AP who are the heads of the departments in which the majority of the study was performed.

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Disclosures

Conflict of interest: none.

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