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Autologous transplantation in multiple myeloma: a GITMO retrospective analysis on 290 patients

IGNAZIO MAJOLINO,* MARCO VIGNETTI,^^ GIOVANNA MELONI,° MARIA LUCE VEGNA,° ROSANNA SCIMÈ,* STEFANIA TRINGALI,* GIOVANNI AMADDII,# PAOLO COSER,# MAURIZIO TRIBALTO,@ ROBERTO RAIMONDI,^ CESARE BERGONZI,§ MARIA ROSARIA SAJEVA,** SIMONA SICA,°° FABIO FERRANDO,## GIUSEPPE MESSINA,@@ FRANCO MANDELLI,° ON BEHALF OF THE GITMO (GRUPPO ITALIANO TRAPIANTI DI MIDOLLO OSSEO)

**Divisione di Ematologia e Trapianti di Midollo Osseo, Ospedale V.Cervello, Palermo; °Dipartimento di Biotecnologie Cellulari e Ematologia, Università degli Studi "La Sapienza", Roma; #Divisione di Ematologia e Centro Trapianti di Midollo Osseo, Ospedale Regionale, Bolzano; @Cattedra di Ematologia, Università Tor Vergata, Roma; ^Divisione di Ematologia, Ospedale S.Bortolo, Vicenza; §Sezione di Ematologia e CTMO, Ospedale di Cremona; **Divisione di Ematologia, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo; °°Reparto di Ematologia, Istituto di Semeiotica Medica, Policlinico A. Gemelli, Roma; ##Centro di Chemioimmunoterapia Intensiva e Terapie Cellulari, Clinica di Medicina Interna I, Università di Genova; @@Divisione di Ematologia, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria; ^^Registro GITMO Autologo, Dipartimento di Biotecnologie Cellulari e Ematologia, Università degli Studi "La Sapienza", Roma, Italy*

ABSTRACT

Background and Objective. **Autologous transplantation is a better treatment for multiple myeloma (MM) than chemotherapy, but uncertainty remains about patient selection, optimal timing of autograft, conditioning regimen, need for a second autograft, and role of maintenance. To provide partial answers to these questions we assessed the results of autologous transplantation in a large cohort of patients whose data were reported to the GITMO registry.**

Design and Methods. **We retrospectively analyzed data from 290 patients with MM (M=150; F=140; median age 52 years, range 19-70; stage I=34, stage II=75, stage III=167) reported to the GITMO. At the time of autograft, 20% were in CR, 66% in PR, while the remaining had non-responsive or progressive disease. Median time between diagnosis and transplant was 16 months (1-90). Seventy-two patients (26%) had been planned to receive a double autograft, but this was actually done in only 35 (12%). The conditioning was chemotherapy in 90%. Peripheral blood was the only source of stem cells in 94%, and purging was applied in 10% of cases. For statistical analysis of data, differences between patient subsets were analyzed using the chi-square test, while the Kaplan-Meier method was used to estimate event-free survival (EFS) and survival (OS) probabilities. The Cox model was used for multivariate analysis.**

Results. **Following the autograft, 116 patients (40%) were in CR, 144 (50%) in PR, 24 (8%) did not respond or progressed and 6 (2%) died before response evaluation. Transplant-related mortality occurred in 3%. At a median follow-up of 23 months, 223 (77%) patients are alive, 71 (24%) of them in CR, and 67 (23%) patients have died at a median time of 20 months (0-70). OS and EFS at 6 years are 47% and 28%, respectively, but the EFS curve shows no plateau. In multivariate analysis, age, β_2-microglobulin level and status at transplant emerged as significant prognostic factors for both OS and EFS, while time from diagnosis to transplant showed borderline significance.**

Interpretation and Conclusions. **Based on the prognostic factors identified in multivariate analysis, we were able to assess the weight of a single prognostic factor or their combinations on transplant outcome. We also calculated the probability of OS and EFS by the number of factors at the time of autograft. Autologous transplantation is a safe and effective procedure, not only in sensitive patients, but also in resistant cases, provided they are <55 years of age and have low β_2-microglobulin. It should be applied *early* after the diagnosis of multiple myeloma, following the delivery of brief primary chemotherapy.**

Key words: multiple myeloma, autologous transplantation, high-dose therapy, prognostic factors

Correspondence: Ignazio Majolino, M.D., Divisione di Ematologia e Centro Trapianti di Midollo Osseo, Azienda Ospedaliera V.Cervello, Via Trabucco 180, 90146 Palermo, Italy.
Phone: international +39-091-6802937 – Fax: international +39-91-6882889.

In recent years, the treatment of multiple myeloma (MM) has been profoundly influenced by the results of high-dose therapy and autologous bone marrow (BM) or peripheral blood stem cell (PBSC) transplantation, with a substantial improvement in the rate of patients achieving remission.[1-3] The number of transplant procedures for MM is steadily increasing.[4] Following the encouraging results of single-arm studies,[5-10] a recent randomized trial[11] demonstrated the superiority of autologous BM

transplantation over chemotherapy in terms of response rate and survival. However, a number of controversies remain concerning the subsets of patients that will benefit most from the autograft strategy, its optimal timing in the course of disease, the best conditioning regimen, the need for a second autograft, and finally the role of maintenance after transplantation.

To assess the clinical results of autologous transplantation, and to evaluate the prognostic influence of pre-transplant characteristics, transplant modalities and post-transplant treatment with respect to response and survival, we have analyzed 290 patients with MM who were autografted in Italy, and whose data were reported to the GITMO (*Gruppo Italiano Trapianto di Midollo Osseo*) Registry. We report here the results of autologous transplantation in this cohort of patients.

Design and Methods

Characteristics of the patients and previous treatments

The analysis was based on the GITMO autologous transplantation registry data. A total of 381 records for autotransplant (324 first, 57 second or further) performed in 324 patients between August 1989 and February 1998 in 18 centers were retrieved. Two hundred and ninety of them fulfilled the minimal criteria required by the study, and were subsequently analyzed. Minimum essential data for analysis were a) age, b) disease status at transplantation, c) response at 100 days of transplantation, and d) follow-up data. There were 150 males and 140 females. Their median age at transplant was 52 years, ranging from 19 to 70. The characteristics of the patients are reported in Table 1. All the data will be reported as related to the 1st autograft procedure, while those concerning a 2nd autograft will be presented under an appropriate heading.

Table 1. Characteristics of the patients.

	No.	*%*
Patients		290
Sex		
M	150	51.7
F	140	48.3
Type		
IgG	171	58.9
IgA	61	21
IgD	3	1
BJ	37	12.7
non secretory	11	3.7
plasma cell leukemia	3	1
other/unknown	4	1.3
Stage at diagnosis		
I	41	14.1
II	90	31
III	155	53.4
unknown	4	0.1
Lines of previous therapy		
1	180	65.2
2	70	25.
≥3	25	9.1
unknown	8	0.4
Response to first line		
CR	32	11.9
PR	196	72.6
NR	3	11.9
PD	8	3
temporary response	2	0.7

Prior to the autograft the patients had received 1 to 8 lines of therapy (median 1), with 90% of cases receiving ≤ 2 lines. After primary treatment 12% achieved a CR and 72% a PR. Overall, in 15% patients the first line of therapy resulted in no reponse (NR, 12%) or progressive disease (PD, 3%). Registry data did not contain information on the type of chemotherapy prior to the autograft procedure, nor on the dose-intensity (standard vs intermediate-high dose) of chemotherapy courses. However, as a consequence of previous treatment(s), at the time of autologous transplantation 20% patients were in CR and 66% in PR. The median time interval between diagnosis and transplant was 16 months, ranging from 1 to 90.

Transplantation procedures

The conditioning regimen consisted of chemotherapy alone in 90% and included TBI in the remaining 10% patients. Melphalan, either alone or in association with other agents, was the mainstay of chemotherapy-based as well as TBI-containing regimens, being employed in 237 out of 287 (82.5%) evaluable patients. The doses of chemotherapy agents and that of radiotherapy included in the conditioning regimen were not available for analysis. PBSC were the only source of stem cells in 94%, bone marrow in 3% and a combination of the two in 3% of the patients. For the purpose of PBSC mobilization into the peripheral blood, 246 patients received a combination of chemotherapy and growth factors, while 16 received chemotherapy and 12 growth factors alone. Some form of purging procedure was applied to autologous stem cell samples in 10% patients.

Hematopoietic recovery and use of growth factors

Recovery of granulocytes was defined as having occurred on the first of 3 consecutive days with a granulocyte count $>0.5\times10^9$/L. Recovery of platelets was defined as having occurred on the first of 3 consecutive days with an unsupported platelet count of $>50\times10^9$/L.

Following the autograft, 241 patients (83%) received a cytokine treatment to hasten engraftment. This was G-CSF in 215 patients, GM-CSF in 12, and a combination of G- and GM-CSF in 6.

Response criteria

The response criteria were those defined by Gore *et al.*[12] CR was the disappearance of myeloma protein,

Table 2. Transplantation procedures. Data are those for 1st autografts. For 2nd autografts see text.

	No.	*%*
Status at transplant		
CR	57	19.7
PR	192	66.2
NR	24	8.3
PD	17	5.9
Single/double autograft		
single	255	87.9
double	35	12.1
Stem cell source		
BM	8	2.8
PBSC	273	94.1
BM + PBSC	9	3.1
$CD34^+$ cell selection		
yes	28	10.3
no	243	89.7
Conditioning		
CT	256	89.8
CT + TBI	29	10.2
Cytokines post-graft		
no	49	17.3
G-CSF	215	76.0
GM-CSF	12	4.2
G- + GM-CSF	6	2.1
other	1	0.4

measured by standard electrophoresis, from both serum and urine, with less than 5% plasma cells in the bone marrow. Immunofixation was not considered. PR was the reduction of serum and/or urinary monoclonal protein to less than 50% the initial value. No response (NR) was the failure to achieve either CR or PR. For patients in PR, progression was at least the 50% increase of monoclonal protein above the lowest achieved level. For patients in CR, relapse was the reappearance of myeloma protein or increase of bone marrow plasma cells. Transplant-related mortality (TRM) was calculated on the basis of deaths not directly attributable to disease occurring within 100 days of transplantation.

Post-transplant therapy

Following the autograft, out of 243 evaluable patients, 166 (68%) received some form of treatment to prevent relapse or progression. This was α-interferon in 143, α-interferon combined with other unspecified drugs in 20, and other unspecified drugs alone in 3; the cumulative proportion of patients receiving post-autograft α-interferon was 67%.

Double autografts

As reported in Table 2, 72 patients (26% of the total) had been planned to receive a double autograft, but this was actually performed within 12 months in 35 of them (12% of the total). Data were available for only 33 (M=15, F=17; median age 53 y, range 35-68). In those patients, the interval between 1st and 2nd transplant was (median) 5 months (range 3-10). The reasons why a 2nd autograft was performed or omitted were not reported by centers. Before autograft 13 of the patients were in CR, 18 in PR and 2 had PD. The conditioning regimen included high-dose melphalan in all. This was combined with TBI in 7, while it was administered as a single drug in the remaining. As the source of stem cells, PBSC alone were employed in 32 patients, a combination of PBSC and bone marrow cells in 1. Thirty patients out of the 33 received G-CSF after the autograft in order to hasten the hematopoietic engraftment.

Statistical analysis

Differences in the distribution of variables between patient subsets were analyzed using the chi-square test. The Kaplan-Meier method was used to estimate EFS and OS probabilities, with differences compared by the two-sided log-rank test.[13] EFS duration was calculated as the interval from date of transplant to the date of last follow-up or of first event. Events were no response, relapse or progression and death from any cause. OS analysis considered death of any cause as an event. In the multivariate analysis using the Cox model, several variables were investigated for possible influence on EFS or OS.[14] Computations were performed using SAS-PC (vers. 6.12; SAS Institute Inc, Cary, NC, USA).

Results

Cells infused and engraftment

Patients autografted with BM received a median of 1.65×10^8/kg nucleated cells (range 0.6-2.1), those autografted with PBSC received a median of 6.0×10^8/kg nucleated cells (range 0.05-68.7), and those autografted with a combination of BM and PBSC received a median of 7.8×10^8/kg nucleated cells (range 2.3-13.9). Time to recovery of 0.5×10^9/L granulocytes was (median) 13 days (range 6-72). Time to recovery of 50×10^9/L platelets was 21 days (range 6-176). Data concerning the recovery of 1.0×10^9 granulocytes and 100×10^9 platelets were not available.

Disease response and transplant-related mortality

Overall response (CR+PR) rate was 97% for patients transplanted in PR, 84% in NR and 69% in PD patients (Table 3). Out of 57 patients autografted in CR, 56 were still in CR at evaluation 90 days after the transplant, 1 was in PR. Concerning patients not in CR at the time of the autograft, CR rate was 28% in PR, 20% in NR and 25% in PD patients. After the autograft, 116 patients (40%) were in CR, 144 patients (50%) in PR, 24 (8%) did not respond or progressed and 6 (2%) had died before response evaluation.

Overall, 8 patients died, 1 from organ failure, 1 from hemorrhage, 2 from infection (1 viral and 1 fungal), 2 from interstitial pneumonia, 1 from VOD and 1 from adult respiratory distress syndrome.

Table 3. Response to the 1st autograft procedure by status at the time of autograft: 275 patients were evaluable for response.

Status	No. evaluable patients	Response		
		CR	PR	Overall
PR	192	54 (28%)	132 (69%)	186 (97%)
NR	25	5 (20%)	16 (64%)	21 (84%)
PD	16	4 (25%)	7 (44%)	11 (69%)

Second autografts

Data about engraftment were reported for 31 of the 33 patients receiving a 2nd autograft, with the recovery of 0.5×10^9/L granulocytes on day (median) 10 (range 8-25) and of 50×10^9/L platelets on day 15 (range 10

Univariate and multivariate analyses

The following factors were analyzed for influence on OS and EFS: sex, age (≤ vs >55 years), monoclonal immunoglobulin type (G vs non-G), β_2-microgloblin levels (≤ vs >4 mg/L) at diagnosis and at transplant, previous lines of treatment (1 vs >1), status at transplant (RC+RP vs NR+PD), months from diagnosis to autograft (≤ vs >6 months), use of TBI in the conditioning regimen, use of cytokines to increase the speed of hematologic recovery following autograft, a double autologous transplant (either planned or performed), the use of a purging technique to deplete tumor cells from the graft, and the post-transplant treatment (mostly α-interferon). β_2-microglobulin at diagnosis, number of treatment lines, status at transplant, time from diagnosis to transplant were found to be significant for OS, while age, status at transplant and interval from diagnosis to transplant for EFS (Table 4). The value of the post-transplant treatment with α-interferon was difficult to evaluate

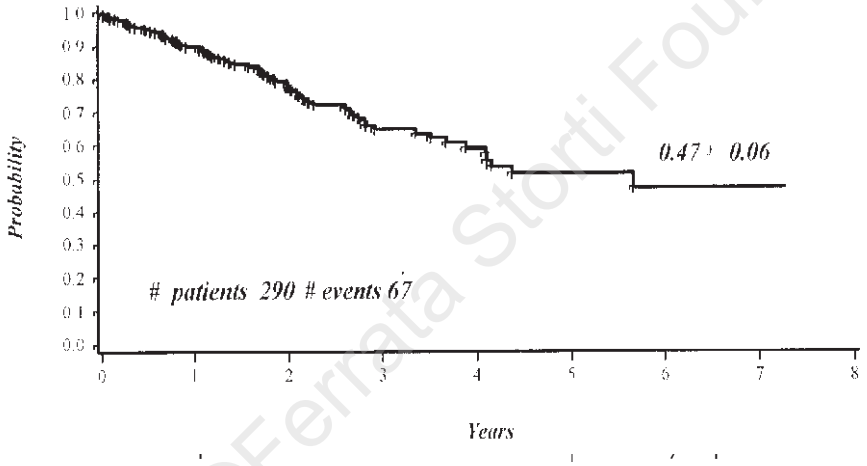

Figure 1. Kaplan-Meier estimate of overall survival (OS) probability among the 290 patients undergoing autologous transplantation. Median OS is 5.6 years. The curve does not show a plateau. The 6-year-projected OS probability is 0.47±0.06.

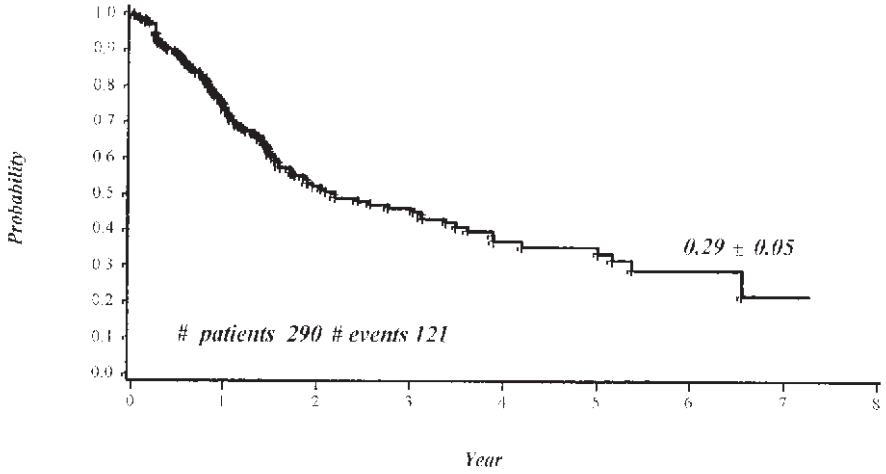

Figure 2. Kaplan-Meier estimate of event-free survival (EFS) probability among the 290 patients undergoing autologous transplantation. Median EFS is 2.2 years. The curve does not show a plateau. The 6-year-projected EFS probability is 0.29±0.05

Table 4. Univariate analysis.

	p value	
	OS	ES
Sex (male vs female)	NS	NS
Age (≤ vs >55 years)	0.09	0.008
Ig type (IgG vs non-IgG)	NS	NS
β_2-microglobulin at diagnosis (≤ vs >4 mg/L)	0.005	NS
Lines of therapy (1 vs >1)	0.005	NS
Status at transplant (RC+RP vs NR+PD)	0.01	0.0001
Time from diagnosis to autograft (≤ vs >6 months)	0.0026	0.02
TBI (no vs yes)	NS	NS
Cytokines post-graft (no vs yes)	NS	NS
Double autograft (planned) (no vs yes)	NS	NS
Double autograft (performed) (no vs yes)	NS	NS
Purging (no vs yes)	NS	NS

OS: overall survival; ES: event-free survival.

Table 5. Multivariate analysis.

	Overall survival	
	RR (95% CL)	p value
Age (≤ vs > 55 years)	2.465 (1.081-5.621)	0.031
β_2-microglobulin (≤ vs >4 mg/L)	2.482 (1.121-5.497)	0.025
Status at transplant (RC+RP vs NR+PD)	2.933 (1.132-7.600)	0.026
Months from diagnosis to transplant (≤ vs >6 months)	7.328 (0.977-54.949)	0.052
	Event-free survival	
	RR (95% CL)	p value
Age (≤ vs > 55 years)	1.975 (1.108-3.519)	0.020
β_2-microglobulin (≤ vs >4 mg/L)	1.915 (1.077-3.406)	0.027
Status at transplant (RC+RP vs NR+PD)	2.702 (1.321-5.530)	0.006

RR = relative risk; CL 95% = 95% confidence limits.

Based on the multivariate analysis results, we also used our regression analysis to generate predicted 2-year probabilities of EFS and OS for subjects not in the study. The survivor function estimates for all combinations of explanatory variables are reported in Tables 6 and 7. Figures 3 and 4 represent the EFS and OS, respectively, by the number of prognostic factors present at the time of autograft.

Table 6. Probability of EFS at 2 years from the autograft for the different combinations of prognostically relevant factors.

	Prognostic factors				
Pattern	Age	β_2	Status	2 y EFS%	95% CL
1	≤55	≤4	CR, PR	64.8	54.0-77.8
2	>55	≤4	CR, PR	42.5	26.8-67.2
3	≤55	>4	CR, PR	43.6	27.9-68.1
4	≤55	≤4	NR, PD	31.0	13.0-73.4
5	>55	>4	CR, PR	19.4	6.4-58.9
6	≤55	>4	NR, PD	10.6	1.5-74.1
7	>55	≤4	NR. PD	9.9	1.9-49.3
8	>55	>4	NR, PD	1.2	0-55.4

CL: confidence limits.

Discussion

We show here the results of a retrospective analysis on a large cohort of patients with MM autografted in Italy. The large majority of them received a single PBSC autograft after high-dose therapy. As expected, the response-rate was high. Forty percent of patients were in CR following transplantation, and 50% in PR. This unusually high response rate may in part be related to the the fact that 20% of patients were already in remission. We suppose this is a consequence of the intermediate-dose regimens employed for PBSC mobilization and collection. Nonetheless, these figures confirm the superiority of high-dose therapy in terms of response, as also demonstrated by the high rate of CR obtained in refractory patients (21% in NR and 25% in PD).

With only 8 out of 290 (2.7%) patients dying of transplant-related causes, our analysis shows a lower TRM than that in other studies[5,9,15,16] in which reported incidences of toxic death range from 8 to 24%. In the literature, TRM was lower only when transplantation was given to the category of responding patients and when it was done early in the course of disease.[11,17] The use of PBSC as the source of stem cells may have contributed to the reduced toxicity found in our analysis. It should be stressed that the present analysis refers to the experience of many centers with different transplantation policies. Better results would be expected from single center studies.

In our study, despite the favorable response in terms of remission, most patients relapsed or progressed. The observed overall survival is 47%, and the event-free survival only 28% at 6 years. In fact, patients continued to progress and die several years after the autograft, with OS and EFS curves failing to show a stable plateau. Similar results were shown in previous studies. In a retrospective analysis of 259 cases[18] the estimated OS and PFS were 50% and 38% at 3 years, respectively, with no survival or remission plateau. The probability of relapse or progression was as high as

Table 7. Probability of OS at 2 years from the autograft for the different combinations of prognostically relevant factors.

	Prognostic factors					
Pattern	Age	β_2	Status	Months*	2 y EFS%	95% CL
1	≤55	≤4	CR, PR	≤6	98.3	94.8-100
2	>55	≤4	CR, PR	≤6	95.8	87.7-100
3	≤55	>4	CR, PR	≤6	95.8	87.4-100
4	≤55	≤4	NR, PD	≤6	95.8	85.2-100
5	>55	≤4	CR, PR	>6	73.1	57.4-93.1
6	≤55	>4	CR, PR	>6	73.0	56.7-93.7
7	≤55	≤4	NR, PD	>6	68.9	47.2-100
8	>55	>4	CR, PR	≤6	89.9	71.5-100
9	≤55	>4	NR, PD	≤6	88.1	66.6-100
10	>55	≤4	NR, PD	≤6	88.2	68.0-100
11	>55	>4	CR, PR	>6	45.9	21.7-97.0
12	≤55	>4	NR, PD	>6	39.7	13.7-100
13	>55	≤4	NR, PD	>6	39.9	16.7-95.1
14	>55	>4	NR, PD	≤6	73.3	37.0-100
15	>55	>4	NR, PD	>6	10.2	1-100

*From diagnosis to transplant; CL: confidence limits.

To assess the prognostic factors in myeloma autologous transplantation, we tried to define a provisional model for clinical use. We first analyzed factors for their influence on EFS and OS. Age emerged as an important prognostic factor in multivariate analysis. Our study included patients with a wide age range (19 to 70 years), with 10% of patients being over 60 years old. The significance for age only emerged at a cut-off value of 55 years. In other studies[5,18,27] in which age was not found to be influential the cut-off was set at 50 years. We also found β_2-microglobulin level at diagnosis to be a reliable predictor of OS and PFS after transplantation. β_2-microglobulin is generally recognized as an important, or even the most important, prognostic indicator in MM patients.[27] Unfortunately, we lack cytogenetic data. The presence of chromosome 11 or 13 abnormalities was the most relevant prognostic variable in the analysis of Tricot *et al.*[28,29] though an unfavorable karyotype is often associated with advanced age and high levels of β_2-microglobulin.

Concerning the optimal time for transplantation,

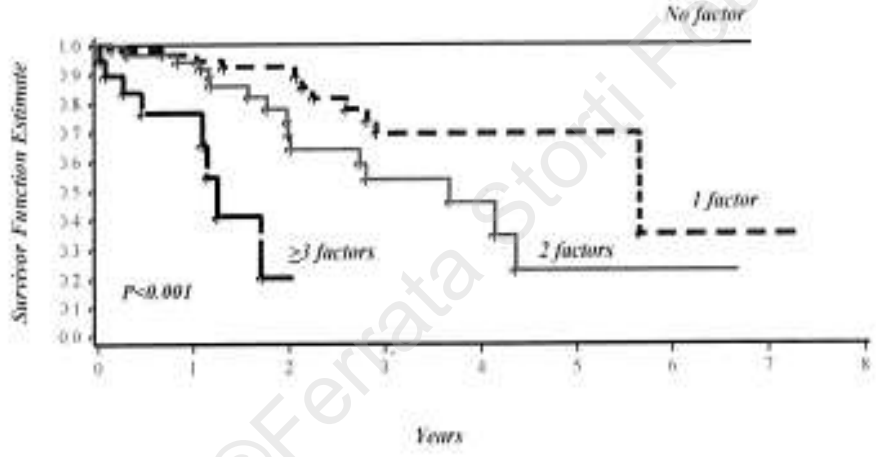

Figure 3. Overall survival by the number of prognostic factors present at the time of autograft (logrank <0.001).

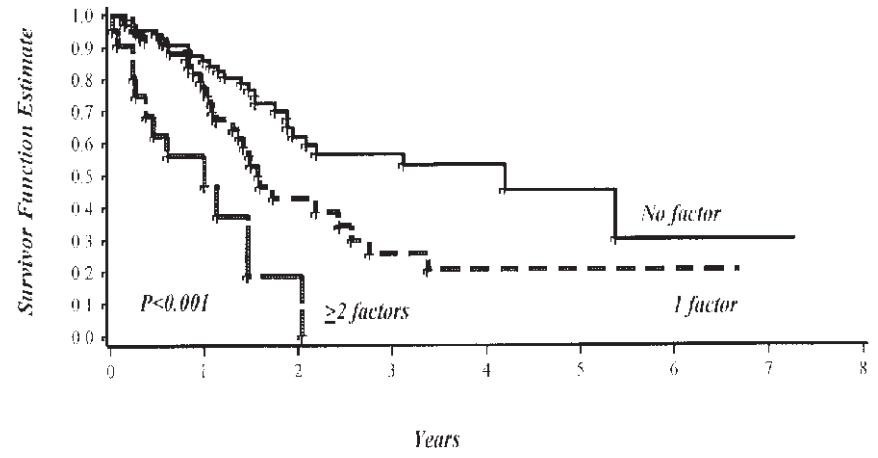

Figure 4. Event-free survival by the number of prognostic factors present at the time of autograft (logrank <0.001).

TBI does not add substantial benefit, at least in this setting.[15,27]

As in other malignant diseases, status prior to the autograft was significantly associated with EFS and OS, in the sense that previously responding patients did better than refractory ones. Nonetheless, refractory patients gain more advantage from transplantation than from chemotherapy. In fact, in the study by Dimopoulos *et al*.[9] patients with primary resistant disease autografted within 8 months reached better results than those on standard therapy. Patients with prolonged (> 1 year) primary resistance and refractory relapse were shown to gain only minimal advantage from high-dose therapy.[10,27] In our study, non-responding patients transplanted <6 months from the diagnosis are projected to survive over 2 years from the autograft, provided they have no more than one of the following additional prognostic factors, age >55 years and β_2-microglobulin level at diagnosis >4 mg/L (see below).

Concerning the use of α-interferon as post-transplant treatment, in our analysis this strategy is associated with a better outcome, in accordance with previously reported data on the activity of this cytokine in multiple myeloma.[30] However, a number of factors may bias the study results when data are analyzed in retrospect, as may the indication for its use and dosage, duration of treatment, and individual tolerance. Also analyzing only cases who were alive and progression-free at 2 months from autograft to reduce the selection bias due to the inclusion of early failures in the non-treated patient group, meant that the group of untreated patients included all those undergoing progression, relapse or death early after transplantation, so that only the subgroup of patients who were alive and free from progression at 2 months was considered. Therefore, the better OS and EFS showed by the α-IFN group should be considered with caution. Only prospective randomized studies can give reliable information on the value of post-transplant treatments.

We also analyzed the EFS and OS probability when there were combinations of various prognostic factors. As shown in Tables 6 and 7, at 2 years the probability of OS is extremely high, lying between 85 and 98%, in remission patients autografted within 6 months of diagnosis, but it may also be high in non-responding patients <55 years of age when the autograft is performed early. On the other hand, results are very poor with 10 to 40% 2-year survival, in patients with >4 mg/L β_2-microglobulin who do not respond to first line therapy. The results for EFS confirm the key role of the previous disease responsiveness. Patients with all the prognostic factors present perform very poorly (1.2% EFS), as do non-responding patients or those with >4 mg/L β_2-microglobulin level at diagnosis (10 to 30% EFS). The negative influence of β_2-microglobulin level seems to be counteracted by a response to first-line treatment. Though the model needs to be validated in prospective studies and on larger cohorts of patients, it is a way of early assessing the weight of a single prognostic factor on transplant outcome. We think it may be reasonably employed by clinicians to make a rough assessment of the life expectation of a given MM patient who is being proposed for autologous transplantation. We also calculated the probability of OS and EFS by the number of factors persent at the time of autograft (Figures 3 and 4).

In conclusion, the data presented here encourage the use of autologous transplantation as a safe and effective procedure in myeloma patients. This applies not only to sensitive patients, but also to resistant cases <55 years of age with a low level of β_2-microglobulin. Our data also support the use of high-dose therapy and autograft *early* after the diagnosis of multiple myeloma, following the delivery of a brief course of primary chemotherapy treatment.

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Disclosures

Conflict of interest: none.

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