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Autologous peripheral blood stem cell transplantation as first line treatment of multiple myeloma: an Italian multicenter study

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ABSTRACT

Background and Objectives. **The outcome of patients with multiple myeloma (MM) has not changed markedly since the introduction of melphalan and prednisone. In recent years several studies have investigated the role of intensive therapy followed by infusion of autologous peripheral blood stem cells (PBSC) together with the administration of hematopoietic growth factors. In this study we evaluated the feasibility and efficacy of a PBSC transplantation program for patients with *de novo* MM in a multicenter setting.**

Design and Methods. **In a non-randomized controlled trial 52 patients with *de novo* MM from 6 Italian centers underwent a three phase treatment strategy including 3 cycles of VAD-like chemotherapy for initial debulking, followed by high-dose cyclophosphamide (HD-CY) and collection of PBSC, that were transplanted after a conditioning regimen with melphalan plus busulfan. Maintenance treatment was a conventional dose of interferon, given until relapse. Actuarial survival and response duration curves were plotted according to Kaplan and Meier's method; the groups were compared using the log rank test. Response rates were compared by the χ^2 test; multivariate analysis was performed according to the stepwise regression model.**

Results. **Overall 39/52 (75%) of patients responded, with a complete remission (CR) rate of 31%. After a median follow-up of 55 months, median duration of event-free survival (EFS) and overall survival (OS) are 21 and 57 months, with 24% and 48% probabilities of being event-free and alive after 6 years, respectively. Among the group of 39 responders, CR was significantly associated with prolonged response and survival (2 deaths and 6 relapses/16 patients) as compared with PR (11 deaths and 15 relapses/23 patients), and remained the only significant variable also in a multivariate analysis. Myelosuppression did not protract beyond one week in transplanted patients; extra-hematologic toxicity was very low.**

Interpretation and Conclusions. **This multicenter study confirms the feasibility of an aggressive approach to *de novo* MM patients. Additional confirmation is given of the increased rate of CR, and the significant prolonged survival observed in complete responders. In this experience the association melphalan plus busulfan was shown to be effective, at least as part of conditioning regimens, in the transplant strategy.**

Key words: multiple myeloma, transplant, peripheral blood stem cells, melphalan, busulfan

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The outcome of patients with multiple myeloma (MM) has not markedly changed since the introduction of melphalan and prednisone (MP), although a large number of prospective studies have evaluated the efficacy of alternative chemotherapy combinations.[1-4] Beginning in the eighties, following the demonstration of a relationship between dose intensity of cytotoxic drugs and tumor response in several hematologic malignancies, the role of high-dose regimens has been investigated in patients with MM.[5-8] To decrease the severe life-threatening hematologic toxicity occurring in patients treated in this way, various hematopoietic stem cell supportive measures have been investigated. While allogeneic bone marrow transplantation can only be applied to younger patients with HLA-identical siblings,[9] autologous stem cell support can be safely used also in older patients with a significant decrease of life-threatening hematologic toxicity and early mortality.[10] The use of peripheral blood stem cells (PBSC), mobilized and collected by means of leukaphereses after high-dose chemotherapy and administration of hematopoietic growth factors,[11] has further shortened the hematopoietic recovery, with a significant decrease of mortality.[10,12] More-

over, the achievement of complete remission (CR), a rare event with conventional treatment, is now observed in an increasing number of MM patients. Most previous trials evaluating transplant programs in MM have been performed on refractory patients, in whom, as expected, the feasibility of treatment and the real impact of such strategies on event-free (EFS) and overall survival (OS), were shown to be limited.[13] However prospective studies including patients with *de novo* myeloma who entered a transplantation program either with autologous bone marrow,[14,15] or PBSC[16] have recently begun to be reported in the literature; their results are encouraging.

Here we report the long term follow-up results of a study whose main objective was to evaluate the feasibility and the efficacy, in a multicenter approach, of a program including myeloablative chemotherapy with hematopoietic autologous peripheral blood stem cell support for the treatment of previously untreated MM patients.

Design and Methods

Patients

From May, 1991 until January, 1996, 52 patients with MM were considered eligible for the study. During the first years patients were enrolled only from 2 centers in Rome (21+14 pts), subsequently another 4 centers progressively entered the study enrolling, before its conclusion, 7, 5, 3, and 2 patients. The selection criteria were as follows: 1) presence of symptoms of the disease, 2) age <55 years (increased to 60 after the first 20 patients), 3) adequate cardiopulmonary function, 4) no previous treatment. The patients' main clinical characteristics are detailed in Table 1: median age was 49 yrs. and 52% of patients were in less than stage III, but they all had clinical symptoms of the disease. The median percentage of bone marrow plasma cells was 47 (range 15-95%) and 34 of the 52 patients had bone lesions; 11 out of 24 evaluable patients had a pre-treatment β_2 microglobulin level >3 mg/L, and 10 had >6 mg/L (median: 2.5; range: 1.1-34.3).

Table 1. Baseline characteristics of patients (n = 52).

Characteristics	*Percentage*
Age > 50 years	48
Male	58
D-S stage	
II	52
III	48
Serum creatinine > 2 mg/dL	4
M component	
IgG	54
IgA	27
IgD	6
Bence-Jones	13
Serum β_2 microglobulin ≥ 3 mg/L	46

Pre-transplant treatment

Patients were treated with 3 cycles of DAV, a VAD-like scheme consisting of vincristine 1.5 mg total dose (td), day 1; adriamycin 50 mg/m^2, day 1; dexamethasone 40 mg td, days 1 to 4, repeated at 28-day intervals. This regimen was chosen because of its lower toxicity and higher feasibility on an outpatient basis. Twenty-eight days after the third cycle of DAV, high dose cyclophosphamide (HD-CY), 7 g/m^2 was administered, followed by G-CSF 5 µg/kg b.w./day s.c., from the first day after the HD-CY until the completion of leukapheresis.

PBSC collection and evaluation

PBSC were collected during 2-5 consecutive leukapheresis, started when the WBC had reached 1×10^9/L. Each sample was investigated by flow cytometry analysis for the presence of cells expressing the CD34 antigen. CFU-GM were assayed in peripheral blood and in each harvested cell suspension before freezing.

Bone marrow harvest

According to the study program, bone marrow was collected in all patients as a rescue measure, but in no case was it subsequently used.

Transplant regimen and post-transplant treatment

The conditioning regimen consisted of melphalan (60 mg/m^2) plus busulphan (4 mg/kg p.o. in divided doses daily for 4 days – total dose 16 mg/kg) followed by the infusion of cryopreserved PBSC. G-CSF 5 µg/kg/day was started from day +1 until the neutrophil count reached 1,000/mm^3 for 2 consecutive days. Treatment with recombinant α2 interferon (IFN) was started after the hematologic reconstitution and continued at a total dose of 3 MU given in divided doses three times a week, until relapse.

Response criteria

Complete remission (CR) was defined as the absence of a detectable monoclonal component (MC) in serum or in urine as detectable by immunofixation analysis, associated with <5% plasma cells in a bone marrow aspirate;

Partial responders (PR) were divided into 2 subgroups: i) PR75 was defined as a decrease of ≥ 75% of the pre-treatment serum values of MC; ii) PR50 was defined as a decrease of ≥ 50% of the pre-treatment serum value of MC and/or ≥ 90% decrease of the Bence Jones protein, combined with a normal clinical condition.

Progression was defined as an increase of at least 25% in the serum MC associated with clear worsening of clinical conditions.

Relapse was defined as reappearance of detectable MC and recurrence of bone marrow infiltration for patients in CR; 50% increase in measurable MC above the "plateau" on two samples 4 weeks apart, for partial responders.

Table 2. Patient flow.

Phase	Start	Removed from study because of:		
		Decline	Progression	Toxicity
DAV	52	3	7	1
CY	41	–	1	1
PBSCT	39	–	–	–
IFN	39	–	21	–

Statistical analysis

Data were analyzed as of January, 1998. EFS was calculated for all patients from the date of diagnosis until the time of disease progression, relapse, death, refusal of treatment or the date the patient was last known to be in remission. OS was defined as the time from diagnosis until death; response duration was evaluated from the time of response to relapse. Actuarial survival and response duration curves were plotted according to Kaplan and Meier's method; the groups were compared by the log rank test. Response rates were compared by the χ^2 test; multivariate analysis was performed according to the stepwise regression model. The following variables were included in the multivariate analysis: age, sex, Durie-Salmon stage, the isotype of MC, serum β_2-microglobulin level, bone marrow plasmacytosis, platelet count, Bence-Jones proteinuria, and response to treatment. Analysis was performed on an intent-to-treat basis.

Results

Patient flow

Patient flow through the whole treatment is depicted in Table 2. Fifty-two consecutive patients have been enrolled through 6 Italian centers: 41 of them completed the first 3 cycles of the program, 3 declined, while 7 were removed because of disease progression and 1 because of toxicity (acute hepatitis C). Forty-one patients received HD-CY: during this phase 2 of them left the study (1 progression, 1 toxicity). Finally 39 patients were transplanted; all of them received IFN as maintenance therapy until they relapsed; after a median follow-up of 55 months 21 patients had relapsed.

Apheresis results

A median number of 3 (range 2-5) aphereses were performed to collect PBSC; the median day when collections were started was +10 (range: 9-14) after the end of HD-CY. The median number of CFU-GM infused was 21.6×10^4/kg b.w. (range 2.1-180.7) while the median number of CD-34$^+$ cells was 15.75 $\times10^6$ (range 1.5-81.5). No relationship was found between the number of PBSC collected and the main characteristics of the patients at diagnosis. The number of infused cells was not predictive of the speed of the hematologic recovery.

Response to treatment

The number of patients responding increased progressively in the different phases of the study (Figure 1). Using an intent-to-treat approach the frequency of >PR (CR) was 58% (4%) after DAV and 77% (11%) after HD-CY. All the 39 patients who underwent the PBSC transplant responded: 16 (41%) obtained a CR, and 23 a partial response, of whom 10 (26%) achieved a PR75 and 13 (33%) a PR50. Considering the whole group of 52 enrolled patients, the percentage of patients responding was 75%, with a CR rate of 31%. Response to DAV was highly predictive of CR: all the 16 patients who achieved CR had previously responded to DAV (14 PR and 2 CR).

Overall, event-free, and disease-free survival

With a median follow-up of 55 months from entry to the study, the median OS of the 52 patients is 57 months, and the median EFS is 21 months; the median response duration of the 39 transplanted patients is 49 months (Figures 2 and 3). Different survivals (even in a multivarate analysis) were not observed between the 13 PR50 and 10 PR75 patients, therefore these were considered together as a single group of partial responders. Considering the 39 responding patients, the 6-year probabilities of being event-free and alive for CR patients are 38% (median EFS=5.7 yrs) and 87%, respectively; while for PR patients these percentages are 26% (median EFS=2.1 yrs; p=0.009) and 44% (median OS=4.5 yrs; p=0.016), respectively (Figure 4).

Post-transplant follow-up

At the date of evaluation 23/52 patients had died. Ten of these deaths had occurred in the 13 patients who had not been transplanted, giving a mortality rate of 78% in this group. Eleven deaths occurred in the 23 partial responders (48%). Finally, 2/16 (12%) patients who achieved CR died, one of whom because of a car accident, still in CR. Fifteen out of 23 partial responders progressed, and 6/16 patients in the CR group relapsed. Response was significant-

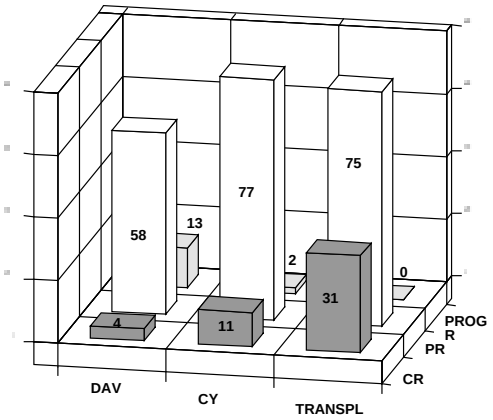

Figure 1. Increase of response rates in relationship to the different phases of the study (*intention to treat*): ≥ PR included both patients who achieved PR or CR. The percentage of CR increased from 4% after DAV, to 11% after CY, to 31% after transplant. All the 16 patients who achieved CR had previously responded to DAV (14 PR and 2 CR).

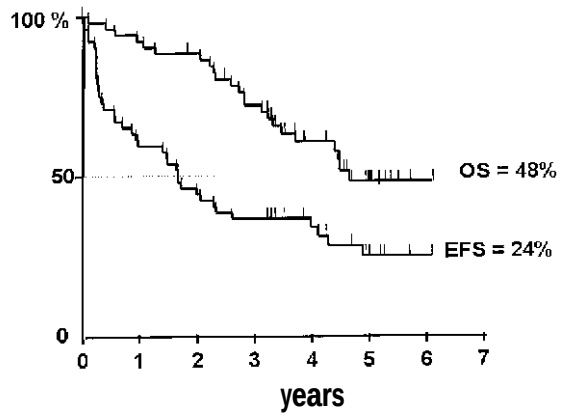

Figure 2. OS and EFS of the 52 patients entered in the study. The median OS was reached at 57 months, whereas median EFS was reached at 21 months. The 6-year probabilities of OS and EFS were 48% and 24%, respectively.

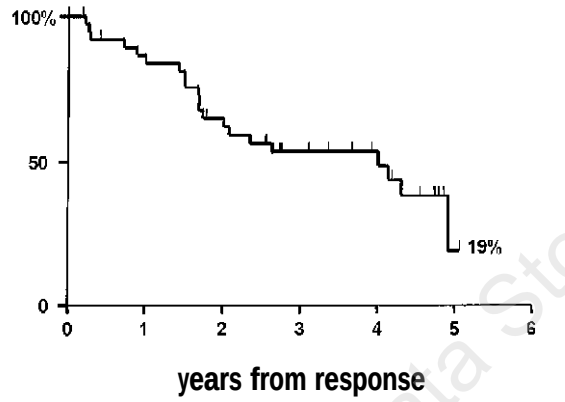

Figure 3. Response duration of the 39 responding patients. The median response duration was reached at 49 months.

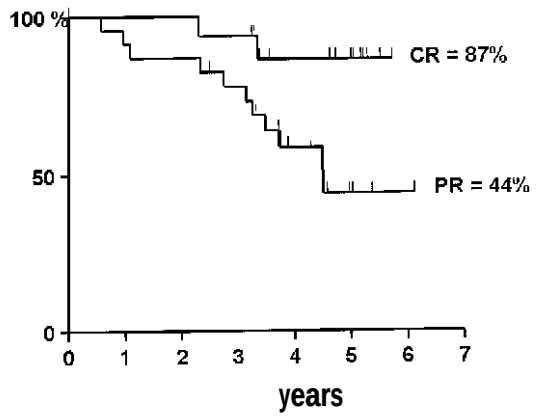

Figure 4. Survival of the 39 responding patients according to the type of response: a significant difference (log rank 0.016) was observed between CR (2/16 deaths, one still in CR) and PR (11/23 deaths).

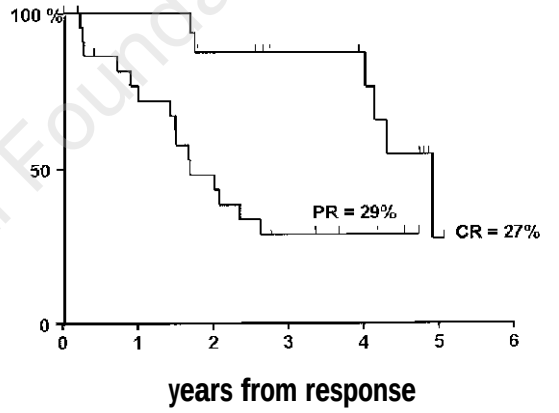

Figure 5. Response duration according to the type of response: response was significantly longer for CR patients (6/16 relapses, median 59 months) than for PR patients (15/23 relapses, median 20 months). Log rank = 0.003

ly longer in patients who reached a CR (median 59 vs. 20 months; p = 0.003) (Figure 5). All the 39 transplanted (and responding) patients were treated with IFN, with a median time to starting IFN of 2 months from transplant (range 1-5). In 3 patients in the CR group serum MC reappeared 7, 11 and 15 months after their transplant, without there being any clinical or histologic evidence of myeloma: the first one is still on treatment with IFN, 52 months after response, while the other 2 had clinical and histologic relapses 50 and 59 months after transplant (39 and 44 months from MC recurrence), respectively. According to the criteria adopted these patients were considered in relapse only at the moment of the histologic relapse.

Prognostic factors analysis

On multivariate analysis of 8 pre-treatment prognostic factors, age <50 years and platelet count >100,000/mm^3 entered in the model of stepwise regression as favorable features for both EFS and OS. In a landmark analysis of 50 patients surviving at least 6 months, response to therapy was the only favorable parameter for EFS (p<0.001), OS (p=0.04), and response duration (p=0.001). When the multivariate analysis was performed only on the 39 responding patients, CR remained the only significant variable for both response duration and EFS (p=0.001). However, it has to be stressed that the initial level of serum β_2-microglobulin was known only for a minority of patients (24/52).

HD-CY and transplant toxicity

The hematologic toxicity was very low; the neutrophil recovery (>500/mm^3) after HD-CY and PBSC transplant occurred on median day +10 (9-13) and +11 (9-12), respectively, while platelets recovered (>20,000 platelets/mm^3) on day +13 (11-15) and +14 (10-18), respectively. In fact, the median duration of severe myelosuppression did not exceed one week. Ten patients after CY and 15 patients after PBSC transplant received 1 and 2 red blood cell transfusions respectively, while the mean number of platelet transfusions required was 1 after HD-CY (3 patients) and 4 after PBSC transplantation (9 patients). The median number of days with fever (>38°C) was 2 (range 1-9) and 2 (range 1-11) after HD-CY and PBSC transplant, observed in 17 and 18 patients, respectively. Extra-hematologic toxicity was also very low: 4 WHO grade 3 episodes and 11 grade 3-4 episodes, mainly gastroenteric and infectious, were observed after HD-CY and PBSC transplant, respectively. Two patients were removed from the study because of toxicity: 1 before HD-CY (acute C hepatitis), one after HD-CY (pulmonary mycobacterium infection); this latter patient was subsequently successfully transplanted.

Two patients, both partial responders, died on day +70 and +155, one due to candida pneumonia, the other because of acute CMV hepatitis.

Discussion

One objective of this study was to evaluate the feasibility, in a multicenter setting, of a PBSC transplantation program for the treatment of newly diagnosed myeloma patients. Although 76% of patients were treated in 2 centers, our results indicate that the program is feasible, as minimal toxicity was observed after HD-CY or PBSC transplant. The toxicity that did occur was mainly myelosuppression, which did not exceed the median duration of 1 week. These results confirm the findings of previous reports[6,12,17,18] on an accelerated hematologic recovery when adequate amounts of autologous peripheral blood progenitor cells were transfused. In this regard it is noteworthy that no patient had to receive the bone marrow harvested as a rescue measure, and the transplant-related mortality during the first 6 months was very low, as only 2 patients (4%) died in PR, 2 and 5 months after transplantation.

The median age of patients treated in our study (49 years) is quite low, compared to that in most series recently published in the literature. This is a consequence of the fact that the design of the study and the selection criteria were discussed among the GITMO centers and approved before 1990, when the low toxicity of high-dose regimens with rescue of PBSC had not been completely appreciated, especially in large series of untreated patients. The median age of patients entered in the tandem transplant program of Barlogie *et al.*[16] in the same period (1990-1995) was 51 years. Nowadays this strategy of high-dose therapy and autotransplantation is also being applied to older patients, as recently reported by Siegel *et al.*,[10] who in a case-matched study of two groups of 49 transplanted MM patients, with median ages of 67 and 52 years, did not observe any difference in feasibility, toxicity and response to treatment between the two differently aged groups. In our study 52% of patients had stage II disease, but all of them had clear symptomatic disease: the median percentage of bone marrow plasmacells was 30% (range 5-90). Sixty percent of the patients had bone lesions. Moreover the stage did not show any significant predictive value for either response achievement or survival. A high percentage of stage II patients (47%) was also observed by Barlogie *et al*.[16] but not by Attal *et al*.[14] in 2 large series of MM patients, but in neither of the 2 studies did the stage have a prognostic value.

There was a high overall response rate (75%; 31% CR) with a median OS of 57 months in the whole group of the 52 enrolled patients. These results are very similar to those observed by the French Myeloma Intergroup[14] in a comparable group of 100 MM transplanted patients

In 231 MM patients enrolled in a *total therapy program* that included 2 consecutive cycles of high-dose therapy, Barlogie *et al*.[16] reported a median EFS and OS of 43 and 68 months, respectively. These favorable results are ascribed by the authors to the additional tumor cytoreduction achieved with the second autotransplant. The importance of substantial tumor regression is also confirmed in our study. Moreover, CR achievement remained, after multivariate analysis, the only significant variable for response duration and EFS. Similarly in the study by Attal *et al*.[14] CR was demonstrated to be the most important prognostic factor for survival. The shorter EFS observed in our study (median 21 months), probably in part depended on an unusually high proportion of patients (25%) being removed from the study during the first 4 months of treatment before the transplant, because of disease progression (8 pts) or refusal (3 pts) (16% before the first transplant in the American study). Six out of 8 patients in progression, and subsequently treated with different strategies, survived more than 2 years (3 patients more than 3 years), suggesting that an early switch to the subsequent high-dose Cy phase could have enabled some of them to recover. We, therefore, decided after this study that patients refractory or progressing during the *pre-transplant phase* should switch to the next scheduled phase of the program.

In our study the median response duration after one transplant (49 months), although in a smaller group of patients, was very similar to that observed by Barlogie *et al*.[16] after two transplant procedures (52 months). These authors give a greater importance to the *dose-dense* therapy administered with the 2 consecutive transplants, rather than attaining CR status; in this regard, however, the significantly prolonged event-free and overall survival of our CR patients should indicate that *dose-dense* therapy with significant tumor cytoreduction can also be achieved after a single treatment with melphalan+busulphan, drugs whose efficacy has already been reported in a study on autologous transplant for CML patients.[19] This drug association was given as conditioning regimen to 24 MM patients in a study by Alegre *et al.*[20] Even though they used different dosages (melphalan, 140 mg/m^2 and busulphan 12 mg/kg), the authors concluded

that the association is safe and feasible, with acceptable toxicity (one transplant-related death), and gives a high objective response rate. Considering the relatively low dosage of melphalan (60 mg/m^2), in our study busulphan (16 mg/kg bw) probably played a major role in the efficacy of the treatment. In two different studies,[21,22] patients with advanced MM received busulphan as part of conditioning regimens in a transplantation program: in both studies patients experienced *unacceptable* toxicity, especially hepatic veno-occlusive disease, when treated with doses of busulphan >12 mg/kg. The absence of relevant liver toxicity in patients treated in our study is probably consequence of the fact that all patients were at the onset of their disease.

All responding patients received IFN as maintenance therapy, this decision being based on our previous results after conventional chemotherapy.[23] According to a first analysis of the results of a study of the Royal Marsden Group[24] performed at a median follow-up of 52 months, this treatment should give a survival advantage, especially to transplanted patients who achieved a CR. However after a subsequent analysis of the same group of patients performed at a median follow-up of 77 months,[25] the survival advantage had *ceased to exist*. Indeed, in our study significantly prolonged OS and EFS were observed for patients who achieved a CR compared to those who raeached a PR, but it was not possible to establish whether IFN had a definite impact on remission and survival duration; only a randomized study could clarify the role of IFN treatment after transplant.

In conclusion this study, although performed on a small number of patients, gives additional support to the feasibility of an aggressive approach, including high-dose treatment with reinfusion of autologous PBSC, as front-line therapy, for patients affected by MM. The association of melphalan plus busulphan proved to be safe and feasible, and we think that its efficacy for treatment of multiple myeloma could be evaluated in larger prospective studies, at least as part of a wider program. In this regard, considering the significantly prolonged remission and survival observed in our study for patients achieving CR after a single transplant, a second consecutive transplant could be reserved only to patients not achieving CR after the first transplant, or at the relapse, for complete responders. In fact, in an ongoing pilot study in our Institution, melphalan plus busulphan are given as a conditioning regimen for a first transplant, while a second transplant, supported by melphalan, 200 mg/m^2, is offered to patients not achieving CR, or at the time of relapse. The efficacy of a late salvage high-dose chemotherapy was recently confirmed by Fermand *et al.*,[13] who observed no difference in survival for patients randomly receiving a transplant as front-line treatment, or at relapse, after conventional chemotherapy. Moreover preliminary results from the study of the French Myeloma Intergroup, in which MM patients are randomly assigned to single or double autotransplant do not show, at an interim analysis, different response rates (EFS or OS) between the two groups of patients.[24]

As of today, autologous transplant for MM patients does not offer a cure; nevertheless the dose-intensity relationship demonstrated in MM patients by an increasing number of reports, together with the observation of larger groups of patients achieving prolonged survival with a better quality of life,[27,28] suggests that the evaluation of more aggressive programs in larger prospective studies in newly diagnosed patients is warranted.

Contributions and Acknowledgments

MT conceived and co-ordinated the study, was responsible for data collection and interpretation and wrote the article; SA conceived the study and contributed to data analysis and paper writing; LC and SS followed-up patients and collected data; TC followed-up the patients and performed progenitor cell cultures. GDP performed the CD34 analysis; GM, GL and GA were involved in the trial design and followed-up the patients; MTP and AP followed patients and collected data; MM and AT conceived the study and contributed to paper writing, GF and IM conceived the study and followed-up patients from their own centers; FM is the senior author: his contribution and supervision were of invaluable help to the study design, data analysis, and critical review. All the authors revised the paper.

The order of the authors reflects their contribution to this study in their own center.

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Disclosures

Conflict of interest: none.

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Potential implications for clinical practice

- Autologous peripheral blood stem cell transplantation as a first line treatment may increase the proportion of MM patients achieving CR.
- Busulfan should be included among drugs of first choice for conditioning regimens of MM patients.

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