Feasibility and outcome of tandem stem cell autotransplants in multiple myeloma

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Background and Objectives. Clinical trials have shown that high dose chemotherapy (HDT) with peripheral stem cell autotransplantation is presently the best treatment for patients with symptomatic multiple myeloma (MM). In the context of an outcomes research project, we analyzed the feasibility of this strategy in clinical practice in a large cohort of consecutive, unselected patients with newly diagnosed MM and looked at the major determinants of response of patients enrolled in a HDT with tandem autotransplantation (*Total Therapy I*, TTI) program.

Design and Methods. Two hundred and fourteen patients were treated outside of a clinical trial and regularly followed-up at our Center for symptomatic MM. Ninety-seven patients (45%) received conventional chemo-radiotherapy regimens, 110 (51%) entered the TTI program and the remaining 7 patients (3.3%) were enrolled in other programs involving HDT with autotransplantation.

Results. Patients enrolled in HDT with tandem autotransplantation programs were 14 years younger and less likely to have co-morbidities than patients treated with conventional therapy. Median overall survivals of the two groups were 60 and 33 months, respectively. Thirteen percent of the patients enrolled in the TTI program did not receive the first HDT with autotransplantation, mostly because of disease progression, and another 16% did not proceed to the second HDT with autotransplantation mainly because of infections or drug-related complications. Most patients achieved complete remission after the second autotransplantation, with acceptable toxicity. However, only patients with a major reduction of the myeloma burden at the end of induction therapy enjoyed significantly prolonged event-free and overall survivals.

Interpretation and Conclusions. Approximately one third of patients with newly diagnosed symptomatic MM completed the TTI program. These data suggest the need to improve the induction therapy in order to increase both the number of patients able to proceed to autotransplantation programs and to enhance the rate of early response.

Key words: multiple myeloma, high-dose therapy, autotransplant, remission, outcomes research.

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Conventional chemotherapy is not a satisfactory treatment for multiple myeloma (MM), since less than 10% of patients so treated attain a sustained complete remission and their median overall survival does not exceed 3 years.[1] Clinical trials have shown that programs including high-dose chemotherapy (HDT) with bone marrow or peripheral stem cell autotransplant increase the complete remission rate up to 50% and prolong the overall survival to a median of about 5 years.[2,3] In particular, randomized, multicenter clinical trials have shown – though not consistently – that the policy of tandem autotransplantation[4] improves both the overall survival and the event-free survival in MM patients compared to the outcomes following a single autotransplantation procedure.[5-8] The applicability of such programs in clinical practice cannot be generalized, since patients enrolled in programs of HDT with tandem autotransplantation are selected for age and lack of concomitant diseases, which can be worsened by high dose chemotherapy. In this respect, the distribution of incident cases of MM by age in Italy for the years 1993-1998 shows a peak of incidence among patients older than 75 years,[9] which is also the population at highest risk of comorbidities. For these reasons, it is difficult to assess to what extent the results of controlled studies can be applied to unselected series of patients. Moreover, these problems are common to most of the hematologic neoplasms and solid tumors.

On this background, in 1999 we launched an outcomes research project in Italy: the Outcomes Research in Oncology (ORO) project, aimed at evaluating patterns of oncologic care and their impact on

long- term outcomes in the main hematologic malignancies and solid tumors. In the context of the ORO study, using the data collected for this purpose, we describe the feasibility and the long-term outcome (up to nine years) of HDT with tandem autotransplantation in a large group of consecutive, unselected patients with newly diagnosed symptomatic MM.

Design and Methods

Source of data

The ORO study was set up in 1999 to evaluate the relationship between patterns of care and long-term outcomes in selected groups of neoplasms. A multidisciplinary panel chose the malignancies to be studied on the basis of their clinical relevance and the complexity of the care provided. For each malignancy the panel also identified process and outcome measures to be evaluated along with socio-demographic and clinical data to define patient care mix and disease staging. Neoplasms identified included breast, colon, lung and prostate cancer, melanoma, lymphomas, leukemias and MM. Data were collected using an *ad hoc* specifically developed data base containing all relevant information. To test the data collection system, information on retrospective patients (all cases admitted between 1997 and 1999) was collected during a pilot phase, lasting one year. Afterwards, from January 2000 we started the prospective phase, with the collection of data of all newly diagnosed patients receiving some or all of their therapy at the Ospedali Riuniti of Bergamo.

Patients

From January 1997 to June 2002 we identified all patients with newly diagnosed symptomatic MM referred to our Institution for treatment. Treatment programs included: radiotherapy only for solitary plasmacytoma; conventional chemotherapy with monthly cycles of melphalan and prednisone,[10] VBAP (vincristine, carmustine, adriamycin, prednisone) or VMCP (vincristine, melphalan, cyclophosphamide, prednisone) schemes;[11] HDT with single or tandem autotransplantation.[4,12]

In the setting of the *Total Therapy I* (TTI) program reported by Barlogie *et al.*[4] induction therapy consisted of three monthly VAD cycles and one cycle of cyclophosphamide followed by granulocyte colony-stimulating factor (G-CSF) (5-10 μg/kg/day) to mobilize $CD34^+$ cells. $CD34^+$ cells were harvested from peripheral blood and underwent negative selection in 39 cases as previously described.[13, 14] Briefly, mature myeloid cells (granulocytes and monocytes) were removed by immune rosetting with anti-CD11b-coated human red blood cells and Ficoll gradient sedimentation using a COBE2991 apparatus and a blood cell processor set. Then, upon labeling with monoclonal magnetic microbeads against CD19, CD56 and CD138 (Miltenyi Biotech, Germany), peripheral blood stem cells were purified by elution through a D-type depletion column and Super-MACS apparatus (Miltenyi Biotech). The plasma cell-depleted fraction of hematopoietic progenitor cells was resuspended in autologous plasma and cryopreserved. Two HDT with melphalan followed by the re-infusion of > 3×10^6 $CD34^+$ cells/kg and G-CSF 5 μg/kg/day were scheduled: the first one month after the end of induction therapy, and the second, with or without total body irradiation (12 Gy in six fractions), three to six months after the first one. We stopped using total body irradiation when evidence accumulated that it increased toxicity without improving patients' outcome.[15] No maintenance therapy was scheduled.

Outcome definitions

Response to treatment, i.e., complete remission, partial remission, no response, disease progression, and relapse, were defined essentially according to Bladè *et al.*[16] In particular, complete remission required negative immunofixation of serum and urine and normal bone marrow trephine. We also included the definition of very good partial remission to indicate a 90% or greater decrease of paraprotein in serum and urine. Response was evaluated after induction therapy and the first and the second transplants. Thereafter, paraprotein, immunoglobin level, proteinuria, serum creatinine, serum calcium, and other hematologic parameters were evaluated every 1-3 months. Bone marrow examination and other tests were performed as needed.

Overall survival was calculated as the time from initiation of therapy to death from any cause or last contact. Event-free survival was calculated as the time from initiation of therapy to either progression of disease or death from any cause or last contact.

Statistical analysis

Survival curves were estimated by the product-limit method and compared using the log-rank test. For univariate analysis, the following variables were considered: sex, isotype (G vs non-G), serum levels of creatinine (<20 vs >20 mg/L), β2-microglobulin (<2.5 vs >2.5 mg/L) and lactate dehydrogenase (<480 vs >480 U/L), C-reactive protein (CRP) (<30 vs >30 mg/L) at diagnosis, negative selection of hematopoietic stem cells, administration of total body irradiation and patients' status at the end of induction treatment, at the first and at the second transplant. Multivariate models were constructed using stepwise regression methods. The following variables were considered: sex, isotype, serum levels of creatinine, β2-microglob-

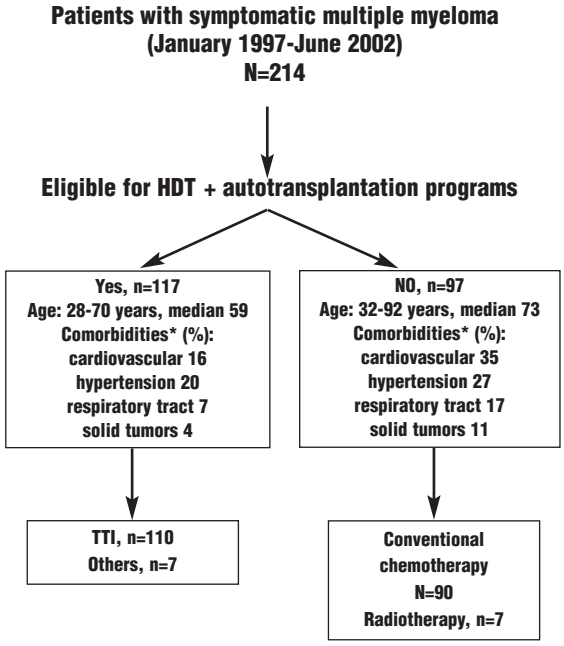

Figure 1. Distribution of 214 patients referred to our Institution for newly diagnosed symptomatic MM according to the treatment program they were considered eligible to receive. *co-morbidities: the same patient may have suffered from more than one concomitant disease.

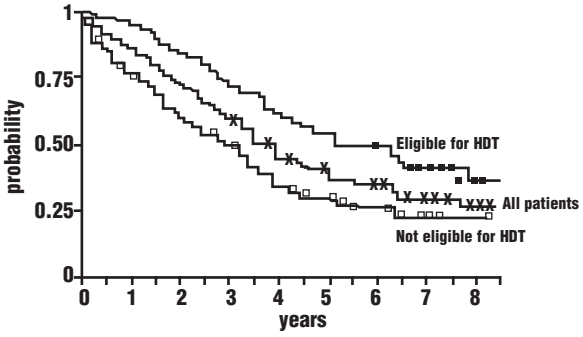

Figure 2. Overall survival (OS) of 214 patients with newly diagnosed MM according to their eligibility for HDT with autotransplantation programs.

ulin and lactate dehydrogenase at diagnosis and status at the end of induction therapy. p values below 0.05 were considered statistically significant.

Results

Patients' characteristics

Two hundred and fourteen patients were referred to our Institution for newly diagnosed symptomatic MM. There were 108 males and 106 females, with a median age of 64 years (range: 28-92). Figure 1 shows the patients' distribution according to the treatment program that they were considered eligible to receive. Ninety-seven patients (45%) received either conventional therapy or radiotherapy only. The other 117 patients (55%) entered programs of HDT with autotransplantation: the TTI program[4] was applied to all but seven of them, who received intermediate dose of melphalan (100 mg/m^2) with tandem autotransplantation according to the program described by Palumbo *et al.*[12] On average, patients enrolled in the HDT with autotransplantation programs were 14 years younger than patients treated with conventional chemotherapy or radiotherapy. Concomitant diseases were less frequent (prevalence 44% and 67%, respectively) and less severe in the former group of patients than in the latter.

As of May 2005, the median overall survival of the 214 patients was 43 months, and 130 of them had died. The median overall survival decreased to 33 months for the 97 patients not eligible for HDT with autotransplantation (70 deaths) and increased to 60 months for the 117 patients who entered the HDT with autotransplantation programs (60 deaths) (Figure 2).

Feasibility of the TTI program

Among the 117 patients eligible for HDT with autotransplantation, 110 were homogeneously treated according to the TTI program described by Barlogie *et al.*[4] Table 1 shows these patients' main clinical and laboratory characteristics. Figure 3 shows the flow of the patients through the TTI program and the reasons for not completing it. Fourteen patients (13%) did not proceed to HDT with melphalan followed by autotransplantation, mostly because of disease progression and death or complications during induction therapy. In two patients it was decided not to proceed to stem cell harvest and subsequent transplantation after three courses of VAD and radiotherapy for plasmacytoma and six courses of VAD for light chain MM. Both of these patients achieved complete remission after completion of treatment. Seventeen patients did not proceed to the second HDT with autotransplantation, mainly because of infections or drug-related complications occurring during or right after the first HDT and transplant. No transplant-related mortality was observed following either the first or the second procedure.

Outcome of the TTI program

After a median follow-up of 48 months (range 2-101), which also includes the five patients who died of disease progression 2-7 months after initiation of treatment, the actuarial overall survival was 50% at 62 months (35% at 101 months), and event-free survival was 50% at 39 months (26% at 101 months). Thirty-four patients survived for more than 60

Table 1. Main clinical and laboratory characteristics of 110 patients with newly diagnosed MM who entered the TTI program.

Characteristics	*Number of patients*
Sex	
Male/Female	58/52
Age, years	
Median (range)	58 (28/70)
Stage (n=109)	
IIA/IIB	12/0
IIIA/IIIB	84/13
Type	
G	60
A	21
Light Chain	22
Non-secretory	5
Plasmacytoma	1
Plasma cell leukemia	1

Serum Parameter	*Median (range)*	*Abnormal*	*% of abnormal*
Creatinine (mg/L)	10 (4.6-106)	(> 20)	9
β2-Microglobulin (mg/L)	2.9 (0.13-16.8)	(> 2.5)	36
Lactate dehydrogenase (U/L)	325 (175-631)	(> 480)	10
c-reactive protein (mg/L)	4 (1-140)	(> 30)	10
Calcium (mg/L)	93 (70-147)	(> 105)	100

Table 2. Event-free survival (EFS) and overall survival (OS) of 110 MM patients 5 years after their enrollment into the TTI program.

Disease status	*No. of patients*	*EFS at 5 years (%)*	*OS at 5 years (%)*
At the end of induction therapy			
Complete remission	17	65*	63
Complete/very good partial remission	29	54°	63
Partial remission/no response	81	24	47
No response	18	27	56
After the first autotransplant			
Complete remission	43	32	50
Partial remission/no response	53	30	58
After the second autoTx			
Complete remission	51	33	59
Partial remission/no response	28	34	63

*Data are shown according to the disease status after induction treatment and after the first and second autotransplants. The prevalence (%) of patients was calculated from the Kaplan Meier curves. *p=0.025 (p was calculated comparing patients in complete remission with patients in all other disease states); °p=0.006 (p was calculated comparing patients in complete or very good partial remission with patients in partial remission and with no response).*

months: 21 of them remain in complete remission (with negative immunofixation) at the time of the present analysis. Two patients died of myelodysplasia while in complete remission. The other 11 patients relapsed: four of them have died. Overall, 54 patients received a second line of treatment for progressive or

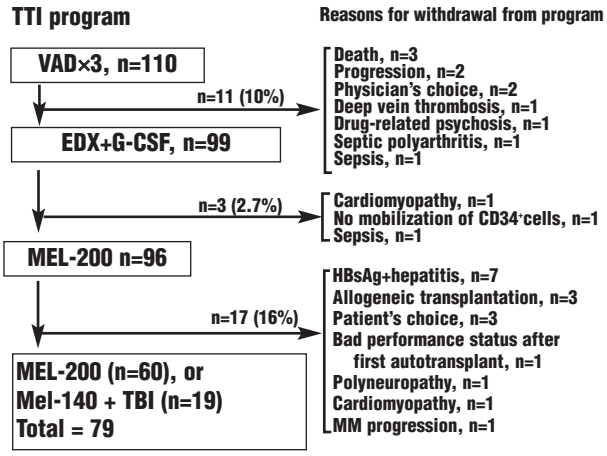

Figure 3. Patients' flow through the treatment and reasons for withdrawal from the program. VAD: vincristine, adriamycin, dexamethasone; EDX: cyclophosphamide (3 or 7 g/m²); G-CSF: granulocyte colony stimulating factor (5 μg/kg/day); Mel-200: melphalan 200 mg/m²; Mel-140 + TBI: melphalan 140 mg/m² plus total body irradiation (12 Gy in 6 fractions).

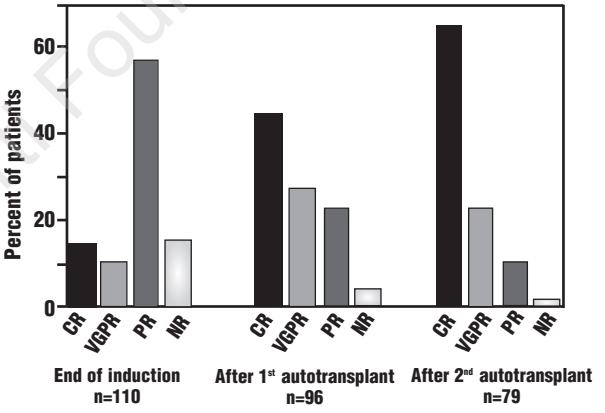

Figure 4. Disease status of 110 MM patients through the TTI program.

CR, complete remission; VGPR, very good partial remission; PR, partial remission; NR, partial remission.

relapsing MM. Thalidomide (either alone or in various combinations) was administered to 31 patients. Seventeen patients (31%) are alive 8-47 months after relapse/progression was documented.

The disease status of patients through the TTI treatment program is shown in Figure 4. Table 2 shows the overall and event-free survival at five years of patients according to their disease status at the end of induction treatment and after the first and the second HDT with autotransplantation. Being in complete remission at the end of induction treatment conferred a significant advantage in terms of event-free survival but only a marginal, not statistically significant, benefit in terms of overall survival (Figure 5). Very similar results were obtained when patients in complete remission

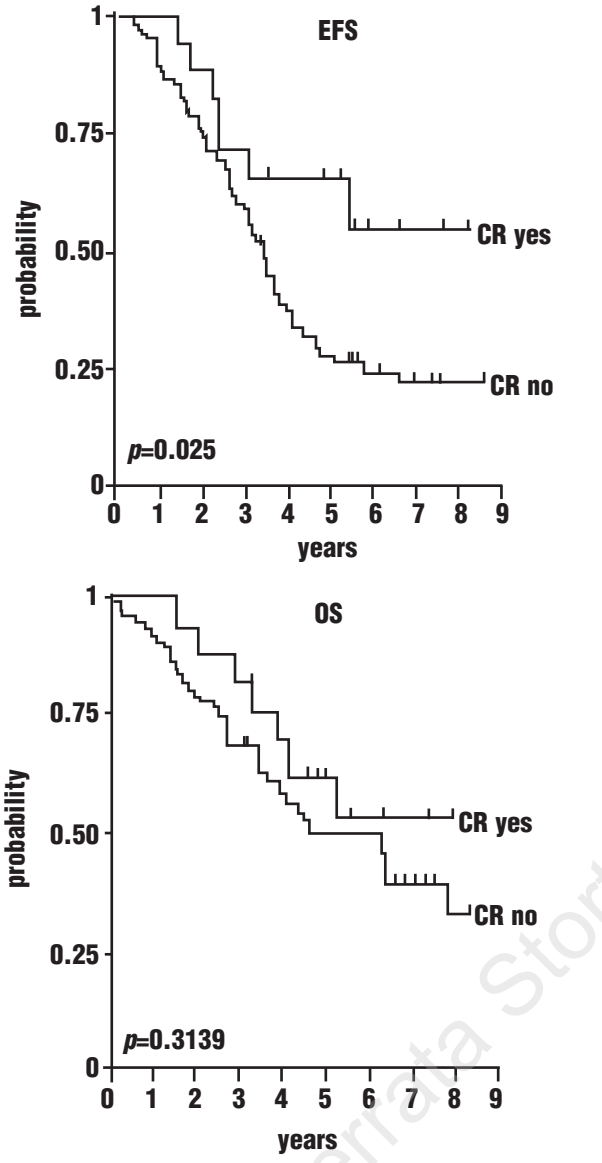

Figure 5. Event-free survival and overall survival of 110 patients with newly diagnosed MM enrolled in the TTI program according to their remission status after induction therapy.

were combined with those in very good partial remission at the end of induction treatment. Reaching complete remission after the first or the second HDT with autotransplantation did not confer a significant advantage in terms of either overall or event-free survival when compared to patients who were not in complete remission at the same time points (Table 2).

Event-free and overall survival were re-analyzed according to a number of variables. Only the G isotype was a significant determinant of better outcome in both univariate (p=0.0273 for event-free survival and p=0.0011 for overall survival) and multivariate (p=0.021 for event-free survival and p=0.005 for overall survival) analysis.

Discussion

Outcomes research should be considered an essential component of clinical research, complementary to randomized clinical trials. It allows an evaluation of how effectively we can deliver medical interventions that have proven to be effective in the context of experimental studies. Moreover, outcomes research is of primary importance for a deeper understanding of medical decision-making in the area of uncertainty or for populations not included in randomized trials. The aim of the ORO project was to document the transferability of the results of randomized clinical trials into the clinical practice of a big Italian hospital and to understand how the degree of transferability could influence patients' outcomes. This work exemplifies the yield of outcomes research when applied in an area in which there are effective treatments, but characterized by complex technologies and serious side effects.

HDT with autotransplantation represents the standard first-line treatment for newly diagnosed symptomatic MM patients. In a systematic review of the literature regarding more than 1,200 MM patients it was shown that HDT with autotransplantation significantly improves the response rate, event-free survival and overall survival compared to those achieved with conventional treatment.[17] Our retrospective analysis of 110 consecutive MM patients treated with HDT with one or, in most cases, tandem autotransplantation confirm these findings. In fact, there was a steady increase in the response rate through the treatment program and 65% of patients were in complete remission after its completion. Their median overall survival is about 5 years, and one third of patients are projected to be alive 9 years after initiation of therapy, in most cases without evidence of disease. These good results closely reproduce those of the Arkansas group,[18] who first introduced the policy of tandem autotransplantation, and those of the InterGroupe Francophone du Myelome.[6] However, they also resemble the data that Bladé and co-workers reported for a group of MM patients with similar characteristics who did not receive an autotransplant.[19] This brings us to consider the issue of the criteria for patients' selection. Compared to the average patient with MM, patients enrolled in programs of HDT with autotransplantation are younger and less likely to have impairment of renal function or serious associated diseases, which may preclude the completion of treatment. Our patients enrolled in the TTI program confirm this, since their median age and prevalence of relevant non-MM-related organ dysfunctions were lower than those of the patients not eligible for the HDT programs (Figure 1). In spite of these favorable

clinical features, 13% of patients enrolled in the TTI program did not proceed to the first transplant, mostly because of toxicity or disease progression. Another 16% of patients did not undergo the second autotransplant, in all but three cases – who received an allogeneic transplant – as a direct consequence of morbidity related to the first autotransplant. This morbidity was mostly represented by acute hepatitis, which developed in HBV DNA-positive patients before lamivudine prophylaxis became available. Overall, about 30% of patients did not complete the program due to treatment toxicity. The program does, therefore, remain toxic, even though no transplant-related deaths occurred. The event-free and overall survival of the 17 patients who received only one autotransplant were similar to those of the entire group, and four of them were in complete or very good partial remission at the time of autotransplantation (*data not shown*).

Taken together, our experience of HDT with tandem autotransplants indicates that the program was feasible in approximately 50% of the cohort of 214 patients with newly diagnosed MM, and was actually completed by about one third of them with manageable toxicity. Fifty-four patients required a second line of treatment due to relapsed/progressive MM. Approximately 30% of them are alive 8-47 months after relapse/progression was documented. This means that HDT with autotransplantation programs does not preclude other treatments from being effective, in particular when new drugs, such as thalidomide,[20] are used.

Response to induction therapy and disease status at the time of autotransplantation have been identified,[21-25] although not consistently,[26-28] as prognostic factors for the program. There is also increasing awareness that patients who achieve complete remission after autologous transplantation are the only ones who seem to benefit from the procedure. As per protocol, our patients proceeded to HDT with tandem autotransplantation irrespectively of their response to induction therapy. This gave us the possibility to compare the outcome of patients in complete remission at the time of the first transplant with that of the other patients. Patients in the former group fared better than patients in partial remission or those who had not achieved any remission of disease (Table 2), confirming the favorable clinical significance of a low tumor burden at the time of autotransplantation. Interestingly, being in complete remission according to stryngently defined criteria (i.e., no detectable paraprotein, negative immunofixation, and <5% bone marrow plasma cells) was not necessary for a favorable outcome in our patients, since when patients with a very good partial remission were combined with those with complete remission, the durations of overall a event-free survival did not change (Table 2). In this respect, we must underline that - despite the progressively increased sensitivity of methods for measuring monoclonal component in serum and urine and for detecting plasma cells in the bone and soft tissues - the concept of complete remission remains elusive in MM. In fact, the monoclonal component level may not correlate directly with the myeloma tumor burden, and localized foci of tumor may not be revealed by random bone marrow aspirates or biopsy. The intrinsic biology of myeloma plasma cells and the host factors responsible for myeloma cell growth and survival are other determinants of outcome of MM patients, none of which is taken into account in the definition of complete remission. We did not have enough cytogenetic or fluorescence *in situ* hybridization data to establish whether and, if so, which abnormality at diagnosis had prognostic value.[29]

The majority of patients with no or partial remission achieved complete or very good partial remission after the first or the second autotransplant, with the median event-free survival approaching 3 years and overall survival slightly exceeding 4 years. This is a strong indication not to withdraw patients from HDT with autotransplantation programs based on an inadequate response to induction therapy, because they too may enjoy prolonged survivals. As they represented the great majority of MM patients in our study, the reduction of myeloma burden at the time of HDT with autotransplantation by modifying the induction therapy. Intensification of chemotherapy such as in the "Total Therapy II" program, described by Barlogie *et al.*[29] and incorporation of drugs such as thalidomide,[20] thalidomide analogs[30] or bortezomib[31] in chemotherapy-based programs may represent strategies through which this goal could be reached in the coming future.

From a methodological point of view, our findings show the importance of observational studies as a strategy of permanent surveillance of oncologic care. They emphasize the utility of routinely collected data not only for the management of patients, but also to produce relevant information regarding the transferability of results from randomized clinical trials into clinical practice and the end results of oncologic care.

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