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Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry

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Background and Objectives. Autologous peripheral blood stem cell (PBSC) transplantation is widely used to treat patients with multiple myeloma (MM). However, only a small fraction of patients remain free of disease in the long-term and most patients will finally relapse. The clinical presentation of relapse after transplantation is very heterogeneous and few reports have analyzed this situation. We report the clinical patterns of relapses after autologous transplantation of 280 patients with MM included in a Spanish Multicenter Registry.

Design and Methods. The medical records of 560 patients with MM transplanted in different centers in Spain, included in the *Spanish Registry of Transplant in Multiple Myeloma*, were reviewed. At diagnosis, 48 (8%) had stage I disease, 143 (25%) stage II and 369 (65%) stage III. The median time from diagnosis to transplantation was 13 months (4-143). The median age was 53 years (23-70). Of the 502 patients assessable for response to intensification therapy after transplantation, 241 (48%) achieved a complete response and 220 (43%) a partial response. The clinical characteristics of 280 patients (52%) who had relapsed after transplantation were retrospectively assessed during long-term post-transplantation follow-up.

Results. At a median follow-up of 23 months, 280(52%) patients had relapsed or progressed after transplantation. The median overall survival was 52 months (SE 8), (CI 95% 37-68) and median estimated progression-free survival was 33 months (SE 2.2, CI 95% 27-38). The median period for relapse was 30 months (2-84) with an actuarial risk of progression or relapse at 60 months after transplantation of 78%. The clinical patterns of relapse were very heterogeneous: 40 cases (14%) presented extramedullary manifestations with multiple plasmacytomas as the main symptoms of relapse, with a minimum or null monoclonal component (MC). In 51 cases (18 %) only an insidious increase of MC protein in serum or urine was detected without other clinical manifestations. In 6 cases (2%) the relapse had criteria of plasmacytic leukemia. The remaining patients presented progressive increase of MC associated with plasmacytic bone marrow infiltration and different clinical myeloma symptoms, mainly new osteolytic lesions. The therapeutic approach was also very heterogeneous, with a global antitumoral response of 30%. Median overall survival after relapse was 14 months (SE 1.4) (CI 95% 11-17).

Interpretation and Conclusions. The patterns of relapse of MM after high-dose therapy are very heterogeneous. The different clinical expressions of relapse may be due to clonal selection after high-dose therapy and could indicate the persistence of a resistant clone. Some patients relapse with extraosseous plasmacytomas without systemic disease. These findings suggest the need for an individualized approach during clinical follow-up after transplantation. Regarding treatment response, patients with myeloma who relapse after high-dose chemotherapy have been classically considered to have few therapeutic options. However, we observed that after different lines of treatment, at least one-third of patients responded, with a median overall survival, after relapse of 14 months. New drugs, such as thalidomide, have been recently proved to be effective in MM patients and could increase the response rate and survival of these patients.

Key words: MM, auto PBSC transplantation, relapse.

In patients with multiple myeloma (MM), high-dose therapy (HDT) followed by autologous peripheral blood stem cell transplantation results in higher complete response (CR) rates and prolonged overall survival compared to conventional chemotherapy treatment.[1-14] For these rea-

sons, this strategy is being increasingly used as front-line therapy for symptomatic MM patients under the age of 70 years and has become the standard treatment for this group of MM patients.[15,16]

Nonetheless, in spite of these results, which have created great expectations in both patients and physicians, most patients eventually relapse and finally die from disease progression.[1-14] The clinical presentation of these relapses is very heterogeneous and little research has focused on this area.[17-20] The purpose of this work was, therefore, to analyze the clinical pattern of relapses or progression after autologous peripheral blood stem cell transplantation of 280 patients with MM included in a Spanish Multicenter Registry.

Design and Methods

The medical records of 560 patients with MM transplanted in different centers of Spain, and included in the *Spanish Registry of Transplants in Multiple Myeloma* were reviewed.[13,14] At diagnosis, 48 patients (9%) had stage I disease, 143 (26%) stage II and 369 (65%) stage III. The median time from diagnosis to transplantation was 13 months (4-143). The median age was 53 years (23-70). After transplantation, of the 502 patients assessable for response to intensification therapy, 241 (48%) achieved CR and 220 (43%) partial response. One hundred and sixty-five of these patients received low doses of subcutaneous α-2-β-interferon after their transplant to prevent relapses. No patient received bisphophonates or steroids as maintenance treatment.

The clinical characteristics of 280 patients who relapsed after transplantation were assessed during the long-term post-transplantation follow-up.

The clinical and biological characteristics of these patients are presented in Table 1.

Table 1. Main characteristics of the patients included in the study.

N	*560*
Age (years) (median/range)	52 (23-70)
Sex	M:342(61%) F:218 (39%)
Monoclonal component	IgG 303 (52%) BJ 98 (17%) gA 142 (25%) Others 37(6%)
Stage at diagnosis	Stage I: 48 (9%) Stage II: 43 (26 %) Stage III: 369 (65%)
Renal insufficiency at diagnosis (Serum creatinine>2 mg/dL)	84 (15%)
β2-microglobulin at diagnosis (median)	2.8 mg/dl (35% > 3)
Time from diagnosis to transplantation, months (median with range)	13(4-143)
Time from diagnosis to transplantation (< 12 months / > 12 months)	275(49%)/285(51%)
Response status pretransplantation	Complete Response: 89 (15%) Partial Response: 346 (63%) No Response: 82 (14%) Progression: 43(8%)
PBSC mobilization method	G-CSF alone 241 (48%) Chemotherapy plus G-CSF 232 (41%) Chemotherapy plus GM-CSF: 37(7%) Chemotherapy alone 18 (3%)
Transplant conditioning regimen	Melphalan: 282(51%) Melphalan plus TBI: 120 (21%) Busulfan plus melphalan : 120(21%) Busulfan plus cyclophosphamide: 27 (5%) Cyclophosphamide plus TBI: I7 (1%)

Response criteria

Response criteria were analyzed according to the EBMT/IBMTR international guidelines.[21] Basically, complete remission (CR) was defined as the absence of a detectable monoclonal component (MC) in serum or in urine by standard electrophoresis and by immunofixation, associated with <5% plasma cells in a bone marrow aspirate. Partial response (PR) was defined as a decrease of > 50 % of the pretreatment serum values 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 a worsening of clinical conditions. Relapse was defined as reappearance of detectable MC on immunofixation or routine electrophoresis and recurrence of bone marrow infiltration for patients in CR or a 50% increase in measurable MC above the *plateau* in two samples collected 4 weeks apart, for partial responders. The development of new lytic lesions or soft tissue plasmacytomas or a definite increase in the size of residual bone lesions were also considered as relapse criteria. Extramedullary relapse was defined as the appearance of an extraosseous plasmacytoma confirmed by histologic study.

Statistical analysis

Event-free survival (EFS) was calculated for all patients from the date of transplantation until the time of disease progression, relapse, death or the

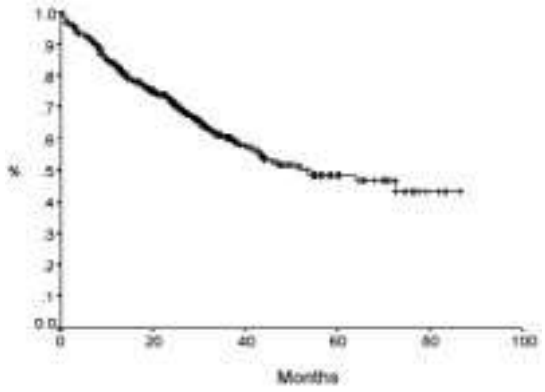

Figure 1. Overall survival (OS) after autologous PBSCT.

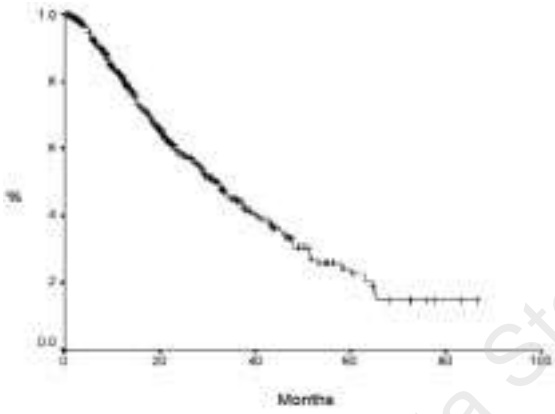

Figure 2. Event-free survival (EFS) after autologous PBST.

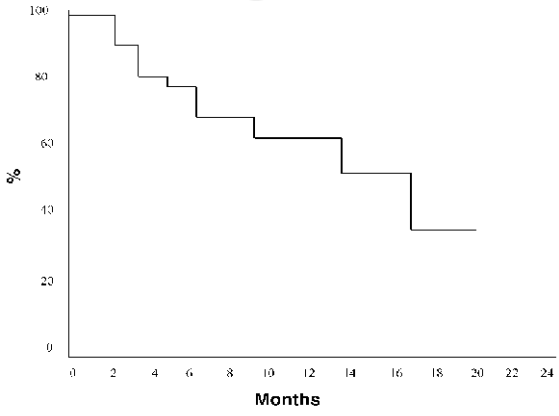

Figure 3. Overall survival (OS) after relapse for the whole group.

date the patient was last known to be in remission. Overall survival (OS) was defined as the time from transplantation until death. Response duration was evaluated from the time of response to relapse or progression. Actuarial survival and response duration curves were plotted according to Kaplan and Meier's method. The groups were compared by the log rank test.[22-24]

Results

At a median follow-up of 23 months, 280 patients had relapsed or progressed after transplantation (55%). The median post-transplant overall survival (OS) was 52 months (SE 8, CI 95% 37-68) and the median event-free survival (EFS) was 33 months (SE 2.2, CI 95% 27-38). The median time until relapse was 30 months (2-84) with an actuarial risk of progression or relapse, projected at 60 months after transplant, of 78% (Figures 1 and 2).

The clinical patterns of relapse were very heterogeneous: 40 cases (14%) developed extramedullary manifestations with multiple plasmacytomas including extramedullary localization as the main symptoms of relapse without monoclonal component (MC) in serum or urine (group 1: plasmacytoma form). The extramedullary plasmacytomas were mainly detected in extraosseous sites by imaging techniques (computed tomography, magnetic resonance imaging) and, when possible, were confirmed by histologic study. These patients' symptoms varied according to the localization of the plasmacytoma.

In 51 cases (18 %) only an insidious increase of MC protein in serum or urine was detected without other clinical manifestations (group 2: insidious form). In 6 cases (2%) the relapse fulfilled criteria of plasmacytic leukemia (group 3: plasmacytic leukemia form) (Table 2).

The remaining patients (183 cases, 66%) showed a progressive increase of MC, and medullary infiltration with different clinical myeloma symptoms, mainly new osteolytic lesions (group 4: classical form). The therapeutic approach in this population was also very heterogeneous depending on the form of relapse (Table 3) with a global antitumoral response of 30%. Median overall survival after relapse was 14 months for the whole group (SE 1.4, CI 95% 11-17). (Figure 3). We observed a significant difference in the OS of patients with the insidious form of relapse and of those with other symptomatic patterns of relapse: the median OS in the indolent form was 18 months ($p < 0.001$) whereas the median OS of patients with the symptomatic forms, plasmacytoma or classical patterns,

Table 2. Clinical patterns of relapses after autologous PBSC transplantation.

Pattern of relapse	*N (%)*
Insidious form	
Increase of MC protein in serum or urine without other clinical manifestations.	51 (18 %)
Classical form	
Progressive increase of MC, medullary plasmacytic infiltration, clinical myeloma symptoms and new osteolytic lesions	183 (66%)
Plasmacytoma form	
Extramedullary manifestations with single or multiple plasmacytomas	40 (14%)
Leukemia form	
Plasmacytic leukemia	6 (2%)

Table 3. Treatment administered for relapse or progression after autologous PBSCT.

Treatment	*N (%)*
No treatment (observation)	23 (20.5%)
Corticosteroids	15 (7%)
Chemotherapy + corticosteroids	15 (7%)
Chemotherapy	88 (37%)
Radiotherapy	8 (4%)
Chemotherapy + radiotherapy	10(5%)
New autologous PBSCT	35(15%)
Allogeneic transplantation	6 (3%)

was about 12 months ($p < 0.001$). The leukemic form had, as expected, the most aggressive course, since the median OS of patients with this form was 5 months ($p < 0.001$). We did not find any correlation between the treatment regimen used or the time to relapse and the different pattern described.

Neither did we find a correlation regarding relapse rates and clinical patterns between patients who underwent maintenance treatment with interferon and those who do not receieve this treatment.

As far as concerns some classical prognostic factors in MM, such as C-reactive protein and β2-microglobulin levels at diagnosis, we did not find any correlation between these and the patterns of relapse. Not enough cytogenetic data were available in this population for a prognostic study.

Discussion

High-dose intensification therapy followed by autologous peripheral blood stem cell transplantation in patients with symptomatic MM has been shown to induce superior disease-free survival and overall survival than conventional chemotherapy.[1-14] However, only a small group of patients achieve durable remissions and most cases relapse at a median of 25-40 months after transplantation.[5,8,12] The patterns of relapse of MM after high-dose therapy are very heterogeneous and usually differ from the clinical presentation of the disease at diagnosis.[17-20] In our opinion, more knowledge in this area would be useful to define prognostic groups in this situation and would also help to administer treatment and anticipate the extension of the disease with drug resistance in patients with subclinical disease. In our study, one group of patients presented with multiple localization of osseous or extraosseus plasmacytomas without significant by plasmacytic bone marrow. Another subgroup of patients had clinical data similar to those found in cases of monoclonal gammopathy of unknown significance (MGUS) with stable disease and long-time sustained presence of serum or urine monoclonal protein without other clinical symptoms. All these cases had the same Ig isotype as at diagnosis. It is also important to study the kinetics of paraprotein clearance after autografting for multiple myeloma in these situations[25] in order to differentiate relapse from oligoclonal proteins or minimum monoclonal components that, in some patients, persist after transplantation and slowly reduce after intensification therapy.

Among the relapses there is a spectrum of heterogeneous patterns ranging from plasmacytic leukemia to classical symptoms. These different expressions of relapse may be due to clonal selection after high-dose therapy and could indicate the persistence of a resistant clone after intensification therapy. These findings suggest the need for an individualized approach in the clinical follow-up of MM patients responding favorably after hematopoietic transplantation, in order to detect very early signs of relapse of progression. For example, the use of imaging techniques including computerized tomography, magnetic nuclear resonance imaging and standard radiography should be emphasized to

detect early relapse presenting as osseous and extraosseous plasmacytomas without plamacytic bone marrow and without expression of protein in serum or urine studies. Early detection of MM activity would allow the administration of therapy before the patient develops any clonal chromosomal alterations with drug resistance mechanisms. We propose a guideline for the periodic review of these cases of MM after transplant. This follow-up review should include, apart from biological studies, thorough general or focalized (if local symptoms are present) imaging studies at least once a year. When identifying new osseous plasmacytomas, previous exploration should be taken into account before considering a relapse, because magnetic resonance imaging may un-mask bone marrow signal changes in responding patients.

Early detection of MM activity would allow the clinical evolution of the relapse to be monitored and help in the decision of whether to administer therapy. The use of new prognostic factors, such as chromosomal findings, are also of interest as recently observed by several groups.[16,26] Regarding treatment response, patients with myeloma who relapse after high-dose chemotherapy have few therapeutic options.[15-20] However, in our series we observed that after different lines of treatment at least a third of the patients responded after relapse with a median EFS of 10 months and a median overall survival of 14 months. These results highlight the need for new strategies to maintain the remission status after transplantation (e.g. interferon, steroids) or the use of new therapies for patients with multiple myeloma such as anti-idiotypic vaccination[27,28] or new molecular-based therapies.[29] For patients who relapse, new drugs with an anti-myeloma effect via other mechanisms such as thalidomide or thalidomide-analogs, have proved effective in patients and open up a new line of approach to improve the poor prognosis of this group of patients.[30]

Contributions and Acknowledgments

AA conceived and co-ordinated the study and wrote the article, AG and CMCH were responsible for data collection and interpretation. JDM and RM contributed to data analysis. JSM and JB contributed to writing the paper. The order of the authors reflects their contribution to this study in their own centers.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Appendix

The following additional centers and investigators also participated in this study. (JL Díaz Martín) Hospital Gregorio Marañon, Madrid; (A Iriondo) Hospital Marqués de Valdecilla, Santander; (C. Pérez-Esquiza) Hospital Virgen del Camino, Pamplona; (R Cabrera) Hospital Puerta de Hierro, Madrid; (J Bessalduch) Hospital Son Dureta, Palma de Mallorca; (C Solano) Hospital Clinico, Valencia; (F. Hernández-Navarro) Hospital de la Paz, Madrid; (L. Hernández Nieto) Hospital Clinico, Tenerife; (J Rifón) Clinica Universitaria, Pamplona; (R Parody) Hospital Virgen del Rocio, Sevilla; (D Carrera) Hospital Virgen de Covadonga, Oviedo; (R Mataix) Hospital NS del Pino, Las Palmas; (G Acebedo) Hospital Vald'Hebron, Barcelona; (JM Moraleda) Hospital Clínico Provincial, Murcia; (JL Bello) Hospital Xeral, Santiago; (J Maldonado) Hospital Carlos Haya, Malaga; (J Constela). Hospital Montecelo, Pontevedra; (L Palomera); Hospital Clínico, Zaragoza; (E Prieto) Fundacion, Jiménez Díaz, Madrid; (JD Mediavilla) Ruber Internacional, Madrid; (L Hernandez-Nieto) Hospital Clinico, Tenerife;(MA Gonzalez) Hospital Xeral Calde, Lugo; (J M Sanchez) Hospital Arnau Vilanova, Lerida; (J M de Pablos) Hospital Virgen de las Nieves, Granada.

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PEER REVIEW OUTCOMES

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received January 24, 2002; accepted April 11, 2002.

What is already known on this topic

Although autologous peripheral blood stem cell transplantation is widely used in the treatment of patients with multiple myeloma, only a small fraction of patients remain disease-free in the long-term while most subjects relapse.

What this study adds

This study shows that the patterns of relapse of multiple myeloma after high dose therapy are very heterogeneous.

Potential implications for clinical practice

Findings of this study indicate the need for an individual approach during clinical follow-up after transplantation.

Mario Cazzola, Editor-in-Chief