Brief report

High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma

Bruno Paiva,[1,2] Norma C. Gutiérrez,[1,2] Laura Rosiñol,[3] María-Belén Vídriales,[1,2] María-Ángeles Montalbán,[4] Joaquín Martínez-López,[4] María-Victoria Mateos,[1,2] María-Teresa Cibeira,[3] Lourdes Cordón,[5] Albert Oriol,[6] María-José Terol,[7] María-Asunción Echeveste,[8] Raquel de Paz,[9] Felipe de Arriba,[10] Luis Palomera,[11] Javier de la Rubia,[5] Joaquín Díaz-Mediavilla,[12] Anna Sureda,[13] Ana Gorosquieta,[14] Adrian Alegre,[15] Alejandro Martin,[16] Miguel T. Hernández,[17] Juan-José Lahuerta,[4] Joan Bladé,[3] and Jesús F. San Miguel,[1,2] on behalf of the PETHEMA/GEM (Programa para el Estudio de la Terapéutica en Hemopatías Malignas/Grupo Español de Mieloma) Cooperative Study Groups

[1]Hospital Universitario de Salamanca, Salamanca, Spain; [2]Centro de Investigación del Cáncer (Instituto de Biología Molecular y Celular del Cancer Universidad de Salamanca-Consejo Superior de Investigaciones Cientificas), Salamanca, Spain; [3]Hospital Clínic, Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain; [4]Hospital 12 de Octubre, Madrid, Spain; [5]Hospital Universitario de la Fe, Valencia, Spain; [6]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [7]Hospital Clínico de Valencia, Valencia, Spain; [8]Hospital de Donostia, San Sebastian, Spain; [9]Hospital Universitario La Paz, Madrid, Spain; [10]Hospital Morales Meseguer, Murcia, Spain; [11]Hospital Lozano Blesa, Zaragoza, Spain; [12]Hospital Clinico San Carlos, Madrid, Spain; [13]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [14]Hospital Universitario Navarra, Pamplona, Spain; [15]Hospital Universitario La Princesa, Madrid, Spain; [16]Hospital Virgen de la Concha, Zamora, Spain; and [17]Hospital Universitario Canarias, Tenerife, Spain

The achievement of complete response (CR) after high-dose therapy/autologous stem cell transplantation (HDT/ASCT) is a surrogate for prolonged survival in multiple myeloma; however, patients who lose their CR status within 1 year of HDT/ASCT (unsustained CR) have poor prognosis. Thus, the identification of these patients is highly relevant. Here, we investigate which prognostic markers can predict unsustained CR in a series of 241 patients in CR at day +100 after HDT/ASCT who were enrolled in the Spanish GEM2000 (n = 140) and GEM2005 < 65y (n = 101) trials. Twenty-nine (12%) of the 241 patients showed unsustained CR and a dismal outcome (median overall survival 39 months). The presence of baseline high-risk cytogenetics by FISH (hazard ratio 17.3; *P* = .002) and persistent minimal residual disease by multiparameter flow cytometry at day +100 after HDT/ASCT (hazard ratio 8.0; *P* = .005) were the only independent factors that predicted unsustained CR. Thus, these 2 parameters may help to identify patients in CR at risk of early progression after HDT/ASCT in whom novel treatments should be investigated. (*Blood*. 2012;119(3):687-691)

Introduction

The incorporation of high-dose therapy/autologous stem cell transplantation (HDT/ASCT) and novel agents in the treatment of young patients with multiple myeloma (MM) has markedly improved the achievement of complete response (CR).[1,2] There are now extensive data in the setting of HDT/ASCT showing that achievement of CR is associated with prolonged survival.[3] Although this is well accepted, the long-term clinical outcome of MM patients who achieve CR is still heterogeneous,[4] and 2 important observations must be made: (1) some patients who revert to a monoclonal gammopathy of undetermined significance (MGUS) stage after therapy experience similar prolonged survival as patients in CR[5]; and (2) a small fraction of patients unexpectedly lose their CR status during the first year after HDT/ASCT and experience a dismal survival rate.[6,7] In fact, survival of patients with unsustained CR is even poorer than for those not achieving CR.[6,7] Herein, we sought to identify prognostic markers predictive of unsustained CR after HDT/ASCT.

Methods

The study included 241 MM patients diagnosed according to International Myeloma Working Group criteria.[8] Patients were included in 2 consecutive PETHEMA/GEM (Programa para el Estudio de la Terapéutica en Hemopatías Malignas/Grupo Español de Mieloma) trials: GEM2000 (VBMCP [vincristine, carmustine, melphalan, cyclophosphamide, and prednisone]/VBAD [vincristine, carmustine, doxorubicin, and dexamethasone] followed by HDT/ASCT and 2 years of maintenance with interferon and prednisone; n = 140) and GEM2005 < 65y (randomized induction with the same chemotherapy plus bortezomib in the last 2 cycles or thalidomide/dexamethasone or bortezomib/thalidomide/dexamethasone followed by HDT/ASCT, and 3 years of maintenance with interferon-α2b or thalidomide or thalidomide/bortezomib; n = 101). All case subjects were in CR at day +100 after HDT/ASCT, defined as absence of the original M component by immunofixation and < 5% plasma cells (PCs) in BM.[9] Patients showing progressive disease within the first year after HDT/ASCT

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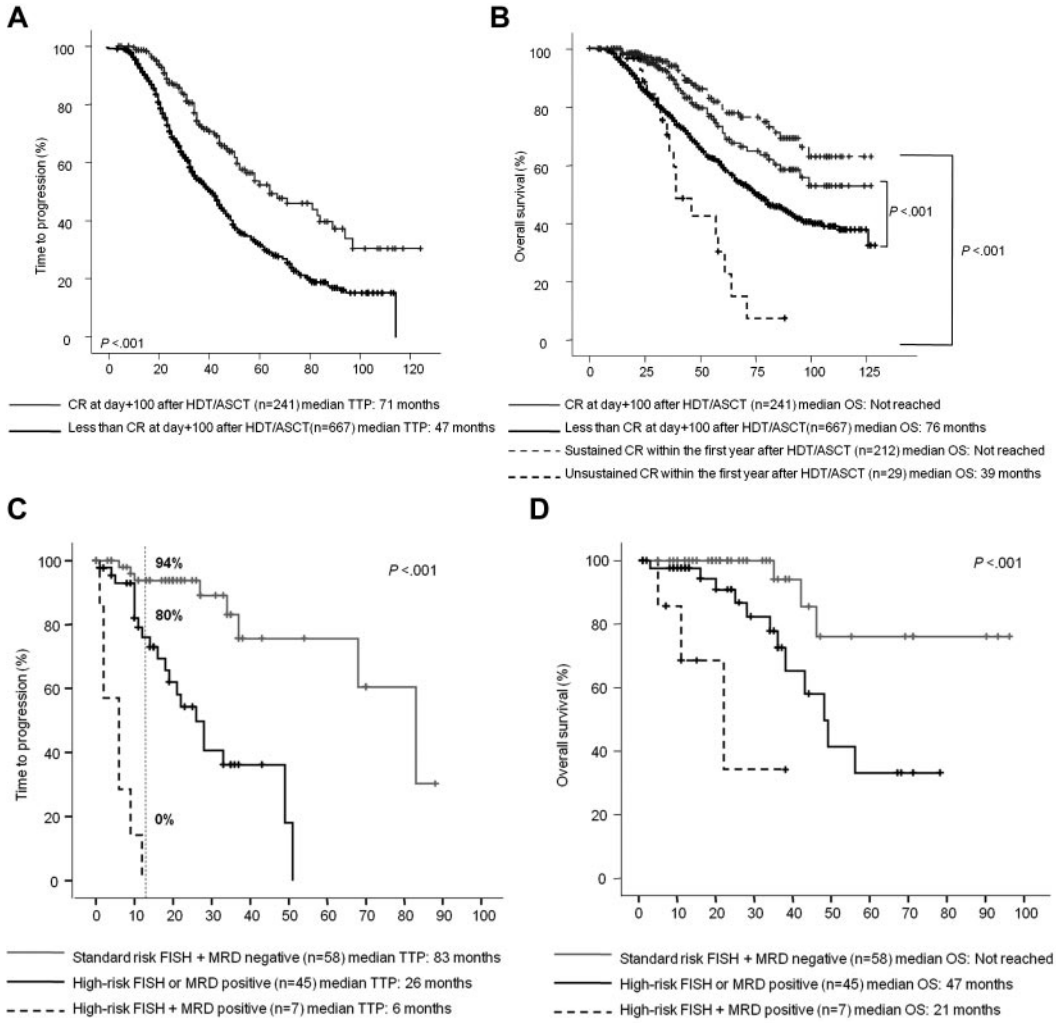

Figure 1. Outcome of patients in CR at day +100 after HDT/ASCT included in the GEM2000 and GEM2005 < 65y trials. (A-B) TTP and OS for patients in CR versus those in less than CR at day +100 after HDT/ASCT. Broken lines in panel B indicate TTP and OS for patients who lost their CR status during the first year after HDT/ASCT (unsustained CR; n = 29 [12%]). (C-D), Landmark analysis for TTP and OS after day +100 after HDT/ASCT of patients (n = 110) in CR according to the pattern of FISH cytogenetics at baseline and immunophenotypic CR status at day +100 after HDT/ASCT.

were classified as having unsustained CR. Median follow-up of the entire series was 49 months.

Erythrocyte-lysed BM samples from 241 patients were immunophenotyped by use of a 4-color (CD38/CD56/CD19/CD45, CD38/CD27/CD45/CD28, and β2-microglobulin/CD81/CD38/CD117) direct immunofluorescence technique. The phenotypic aberrancies detected at diagnosis allowed normal PCs and myelomatous PCs to be discriminated, as described elsewhere,[10] and were used as patient-specific probes for minimal residual disease (MRD) assessment at day +100 after HDT/ASCT.[11] Patients were defined as being in immunophenotypic CR[12] when myelomatous PCs were undetectable by multiparameter flow cytometry (MFC) at a sensitivity of $\leq 10^{-4}$ to 10^{-5}.

FISH was performed at baseline in immunomagnetic-enriched PCs from 110 case subjects. Patients harboring a t(4;14), t(14;16), or del(17p) were classified as having high-risk disease and all other cases as being at standard risk, according to International Myeloma Working Group guidelines.[13] Conventional cytogenetics were not part of the GEM2000 and GEM2005 < 65y workload; therefore, abnormalities on chromosome 1 or 13 were not a criterion to define high-risk patients. Samples were collected after informed consent was obtained in accordance with the Declaration of Helsinki and with approval from the ethics committees of all participating institutions.

The χ^2 and Mann-Whitney U tests were used to estimate statistically significant differences. Survival curves were plotted by the Kaplan-Meier method, with differences assessed with the log-rank test. For multivariate analysis, stepwise Cox proportional hazard and logistic regressions were performed with SPSS Version 15.0 software (SPSS Inc).

Results and discussion

Time to progression (TTP; median 71 months) and overall survival (OS; 71% at 5 years) of patients in CR were longer than those in less than CR at day +100 after HDT/ASCT (TTP: median 47 months, $P < .001$; Figure 1A; OS: 60% at 5 years, $P < .001$; Figure 1B). Nevertheless, the baseline characteristics of the 241 patients in CR did not differ greatly from those not achieving CR at day +100 after HDT/ASCT (data not shown).

We first investigated which of the most relevant disease characteristics had prognostic influence in patients in CR at day +100 after HDT/ASCT. In the present study cohort, some of the markers with consistent influence in unselected myeloma populations, such as patient age, International Staging System disease stage, serum albumin and β_2-microglobulin, BM PC burden, percentage of PCs in S phase, and the achievement of CR after induction, were not of significant predictive value (Table 1). In addition, the type of induction was not of significant prognostic value in this selected population of patients in CR at day +100 after

Table 1. Patients in CR at day +100 after HDT/ASCT: disease features with a significant effect on TTP or OS (univariate and multivariate analyses)

	Univariate analysis				Multivariate analysis			
	TTP		OS		TTP		OS	
	3 y, %	*P*	3 y, %	*P*	HR	*P*	HR	*P*
Induction		.9		.4	—	—	—	—
VBMCP/VBAD	72		90					
VBMCP/VBAD/ bortezomib	79		100					
TD	80		100					
VTD	79		92					
ISS disease stage		.5		.08	—	—	1.0	.9
I or II	77		95					
III	60		75					
Age, y		.5		.06	—	—	3.5	.03
Younger than 60	77		90					
≥ 60	70		90					
Hemoglobin, g/L		.07		.01	1.2	.6	2.0	.2
> 100	78		94					
≤ 100	69		83					
Serum albumin, g/L		.3		.2	—	—	—	—
> 35	79		90					
≤ 35	53		87					
Serum β2-microglobulin, mg/L		.4		.7	—	—	—	—
≤ 3.5	76		93					
> 3.5	64		81					
BM PCs, %		.2		.9	—	—	—	—
< 30	79		94					
≥ 30	66		93					
% PCs in S phase		.2		.1	—	—	—	—
< 2	86		98					
≥ 2	73		91					
Interphase FISH cytogenetics		< 001		.07	6.4	< .001	4.3	.03
Standard risk	80		96					
High risk*	40		73					
Response before HDT/ASCT		.1		.8	—	—	—	—
CR	75		93					
No CR	68		89					
MRD status by MFC		< .001		.001	7.7	< .001	6.6	.003
Immunophenotypic CR	86		98					
No immunophenotypic CR	58		80					
Maintenance		.006		.08	5.1	.1	1.2	.9
Interferon/prednisone	74		89					
Interferon-α2b	60		87					
Thalidomide	87		94					
Bortezomib/thalidomide	84		100					

VBMCP/VBAD indicates vincristine, carmustine (BCNU), melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, and dexamethasone; TD, thalidomide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; ISS, International Staging System; and —, not included in the multivariate analysis.

*High-risk cytogenetics includes any t(4;14), t(14;16), or del(17p); standard-risk cytogenetics includes all other cases.

HDT/ASCT. In contrast, significant differences according to the type of maintenance therapy (interferon/prednisone versus interferon-α2b versus thalidomide versus thalidomide/bortezomib) were noted for TTP (74% vs 60% vs 87% vs 84% at 3 years, respectively; $P = .006$), as was a trend for OS (89% vs 87% vs 94% vs 100% at 3 years, respectively; $P = .08$), whereas the presence of baseline anemia was a significant prognostic marker for OS ($P = .01$). With regard to cytogenetics, 16% of CR patients were considered to have high-risk disease at presentation and showed a significantly inferior TTP (3 years, 40% vs 80%; $P < .001$) and borderline OS (3 years, 73% vs 96%; $P = .07$) compared with case subjects with standard risk. In addition, MFC immunophenotyping showed persistent MRD in 87 (36%) of the 241 CR patients, and the failure to achieve an immunophenotypic CR at day +100 after HDT/ASCT resulted in significantly inferior TTP (3 years, 58% versus 86%; $P < .001$) and OS (3 years, 80% vs 90%; $P = .001$). In the multivariate analysis, the best combination of independent predictive parameters for TTP was immunophenotypic CR status ($P < .001$; hazard ratio [HR] 7.7) and FISH cytogenetics ($P < .001$; HR = 6.4); in turn, for OS, immunophenotypic CR status ($P = .003$; HR = 6.6), FISH cytogenetics ($P = .03$; HR = 4.3), and age ≥ 60 years ($P = .03$; HR = 3.5) were selected.

Results with novel induction regimens showed similar CR rates for high- and standard-risk cytogenetic cases,[14-17] although the former population usually shows shorter progression-free survival,[14-18] which reinforces the need for additional tools for early identification of unsustained CR. In line with previous observations,[10,11,19-22] we have shown that when highly sensitive techniques are used, persistent MRD is still detectable in an important fraction of patients in CR after HDT/ASCT. We further explored the clinical

impact of the immunophenotypic CR in the context of standard-risk and high-risk disease. As expected, the best prognosis was for patients with both standard-risk cytogenetics and achievement of an immunophenotypic CR (3 years: TTP 94%, OS 100%), whereas the worst outcome occurred in cases with both high-risk disease and persistent MRD (3 years: TTP 0%, OS 32%; $P < .001$). The 2 other categories had an intermediate prognosis, with no significant differences between the subgroup with high-risk cytogenetics who achieved an immunophenotypic CR (3 years: TTP 69%, OS 100%) and patients with standard-risk disease but who failed to achieve an immunophenotypic CR after HDT/ASCT (3 years: TTP 57%, OS 90%; $P = .5$).

After this analysis of the overall population of patients in CR, we investigated the parameters that could help to identify patients in CR at risk of early relapse (≤ 1 year) after HDT/ASCT. Of the 241 patients, 29 (12%) progressed within 1 year after HDT/ASCT (unsustained CR), and this subgroup was investigated further. In agreement with previous observations,[6,7] patients in the present series with unsustained CR showed a dismal outcome, with a median OS of only 39 months ($P < .001$; Figure 1B). Information on the salvage therapy of these 29 patients is included in supplemental Table 1 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Patients with unsustained CR had a significantly higher incidence of anemia at baseline (50% vs 26%, $P = .008$), advanced International Staging System stage II or III (85% vs 56%, $P = .005$), high-risk cytogenetics (42% vs 10%, $P = .002$), and persistent MRD by MFC (66% vs 32%, $P = .001$) compared with the remaining cases. In addition, patients scheduled to receive interferon-α2b without prednisone showed a significantly increased frequency of unsustained CR versus those scheduled to receive other regimens (26% vs 9%, $P = .01$). Previous observations[23] have suggested that patients who demonstrate an early response to therapy may be associated with an aggressive MM and poor prognosis; however, this was not observed in the present study, because patients with unsustained CR showed a trend toward lower CR rates before HDT/ASCT (33% vs 54%; $P = .061$). On multivariate analysis, only the pattern of cytogenetic abnormalities ($P = .002$, HR = 17.3) and the immunophenotypic CR status at day +100 after HDT/ASCT ($P = .005$, HR = 8.0) emerged as independent predictive markers for unsustained CR. Of note, when the 3-year cutoff previously reported by the Arkansas group[6,7] was used to define unsustained CR after HDT/ASCT, this subgroup of patients (n = 64; 27%) showed a poor outcome, albeit better than that of patients who lost their CR status within the first year (median OS of 58 vs 39 months; $P = .03$). On the basis of these 2 variables, we established a predictive index by assigning 1 point for each adverse factor. Accordingly, 3 risk groups of patients in CR after HDT/ASCT were defined, with significantly ($P < .001$) different rates of disease progression (Figure 1C) within the first year after HDT/ASCT for patients with none, 1, or both of the risk factors (median TTP of 83, 26, and 6 months, respectively). This predictive index according to FISH cytogenetics and MRD status by MFC also had a clear effect on OS of patients in CR at day +100 after ASCT (Figure 1D).

The results of the present study show that the baseline evaluation of cytogenetic abnormalities combined with response assessment by MRD can discriminate a subset of CR patients with a dismal outcome who should be candidates for novel treatment strategies after HDT/ASCT.

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Authorship

Contribution: B.P., M.-B.V., M.-A.M., and L.C. analyzed the flow cytometric data; N.C.G. analyzed the FISH data; L.R., J.M.-L., M.-V.M., M.T.C., A.O., M.-J.T., M.-A.E., R.D.P., F.D.A., L.P., J.D.I.R., J.D.-M., A.S., A.G., A.A., A.M., M.T.H., J.-J.L., J.B., and J.F.S.M. contributed with provision of study material or patients; J.-J.L., J.B., and J.F.S.M. conceived the idea and together with L.R., M.-B.V., and M.-V.M designed the study protocol; B.P., J.-J.L, J.B., and J.F.S.M. analyzed and interpreted data; B.P. performed statistical analysis; B.P., J.-J.L, J.B., and J.F.S.M. wrote the manuscript; and all authors reviewed and approved the manuscript.

Conflict-of-interest disclosure: B.P., A.O., F.D.A., L.P., and J.-J.L. have received honoraria from Celgene and Janssen-Cilag; L.R. has received honoraria from and served on the advisory board for Janssen-Cilag and Celgene; M.-V.M. has served on the speakers' bureau for Millennium, Celgene, and Janssen-Cilag; J.B. has received honoraria from and served on the advisory board for Janssen-Cilag and Celgene and has received grant support from Celgene and Janssen-Cilag; and J.F.S.M. has served on the speakers' bureau and on the advisory board for, and has received honoraria from, Millennium, Jansen-Cilag, and Celgene. The remaining authors declare no competing financial interests.

Correspondence: Professor Jesús F. San Miguel, Hospital Universitario de Salamanca, Paseo de San Vicente 58-182, 37007 Salamanca, Spain; e-mail: sanmigiz@usal.es.

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