Brief report

A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma

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One hundred ten patients with multiple myeloma (MM) failing to achieve at least near-complete remission (nCR) after a first autologous stem cell transplantation (ASCT) were scheduled to receive a second ASCT (85 patients) or a reduced-intensity-conditioning allograft (allo-RIC; 25 patients), depending on the human leukocyte antigen (HLA)–identical sibling donor availability. There was a higher increase in complete remission (CR) rate (40% vs 11%, $P = .001$) and a trend toward a longer progression-free survival (PFS; median, 31 months vs not reached, $P = .08$) in favor of allo-RIC. In contrast, it was associated with a trend toward a higher transplantation-related mortality (16% vs 5%, $P = .07$), a 66% chance of chronic graft-versus-host disease and no statistical difference in event-free survival and overall survival. Although the PFS plateau observed with allo-RIC is very encouraging, this procedure is associated with high morbidity and mortality, and therefore it should still be considered investigational and restricted to well-designed prospective clinical trials. This trial is registered at ClinicalTrials.gov ID number NCT00560053 (Blood. 2008;112:3591-3593)

Introduction

Autologous stem cell transplantation (ASCT) has become the standard of care in the up-front therapy for younger patients with multiple myeloma (MM).[1-3] In 2 randomized trials, double ASCT was superior to a single transplantation in patients failing to achieve complete remission (CR) or very good partial response after the first transplantation.[4,5] However, despite tandem ASCT, patients continue to relapse and there is no survival plateau. Allogeneic stem cell transplantation is the best potential curative approach.[6,7] However, a transplantation-related mortality (TRM) rate of 30% to 50% constitutes its major limitation.[6-8] The use of dose-reduced intensity conditioning (allo-RIC) has reduced the TRM to 10% to 20%.[9-15] Interestingly, promising results with autograft followed by an allo-RIC have been reported.[11,13] However, only 2 trials comparing the efficacy of double ASCT versus a single autograft followed by an allo-RIC have been published and they show contradictory results.[14,15] We report the results achieved with a second ASCT versus allo-RIC in chemosensitive patients failing to achieve CR or near-complete remission (nCR) after a first ASCT.

Methods

Patients and treatment plan

Patients diagnosed with symptomatic MM between October 1, 1999, and December 31, 2004, who were younger than 70 years were included in the Programa para el Estudio y la Terapéutica de las Hemopatías Malignas y Grupo Español de Mieloma (PETHEMA/GEM)–2000 trial. They received 6 cycles of vincristine, carmustine (BCNU), melphalan, cyclophosphamide, prednisone (VBMCP)/vincristine, BCNU, adriamycin, dexamethasone (VBAD) chemotherapy[16] followed by a first ASCT. Patients failing to achieve CR or nCR (ie, persistence of a serum or urine M-protein on the electrophoretic pattern) were scheduled to receive either a second ASCT conditioned with CVB (cyclophosphamide, etoposide, BCNU) or melphalan (MEL)–200 or an allo-RIC conditioned with fludarabine 25 mg/m^2 for 5 days and melphalan 70 mg/m^2 for 2 days. The treatment assignment to a second autologous transplantation or to an allo-RIC was based on the availability or not of an HLA-identical sibling donor among patients younger than 65 years. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A and methotrexate.

Of 752 patients who received a first ASCT, 278 (37%) achieved CR, 124 (16%) nCR, 280 (37%) partial response, 45 (6%) stable disease, and 25 (3%) progressive disease. Of the 280 responders failing to achieve CR or nCR, 170 did not undergo the preplanned second transplantation for the following reasons: patient refusal (47), insufficient progenitors (29), PD (27), poor performance status (25), physician decision (23), and unknown (19). The remaining 110 patients underwent the planned second transplantation; 85 received a second ASCT (65 with CVB and 20 with MEL-200) and 25 an allo-RIC. This study was approved by the ethics committee of Hospital Clinic IDIBAPS and informed consent was obtained from patients in accordance with the Declaration of Helsinki.

Diagnostic and response criteria

The diagnosis of MM was established according to the criteria of the Chronic-Leukemia Myeloma Task Force.[17] Response, relapse, and progression were

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Table 1. Characteristics of the patients at diagnosis and response status at second transplantation in each group

	2nd ASCT group, n = 85	Allo-RIC group, n = 25
Age*, y (mean ± SD)	55 ± 8	52 ± 6
Hemoglobin, g/dL (mean ± SD)	10.5 ± 2.3	9.9 ± 2
Serum creatinine, mg/dL (mean ± SD)	1.2 ± 0.9	0.9 ± 0.16
Serum calcium, mg/dL (mean ± SD)	9.6 ± 1.6	9.4 ± 0.65
Albumin, g/dL (mean ± SD)	3.5 ± 0.79	3.6 ± 0.7
B2 microglobulin, mg/L (mean ± SD)	3.9 ± 3.2	3 ± 1.3
ISS		
1	31	11
2	39	9
3	13	1

ISS indicates International Staging System.
*All *P* values were not significant except a trend for age ($P = .07$).

assessed according to European Bone Marrow Transplant (EBMT) criteria,[18] adding the nCR category (negative electrophoresis with positive immunofixation).

Statistical methods

The Kaplan-Meier method was used to plot the survival curves,[19] which were compared by the log-rank test.[20]

Results and discussion

As in some other trials on tandem transplantation,[15,21] a limited feasibility with a high proportion of dropouts, mainly due to patient or physician preference, was observed in our series. In patients who underwent a second ASCT, the CR rate for CVB was lower than with MEL-200 (3% vs 35%, $P < .001$). However, there were no differences in progression-free survival (PFS; median, 33 months vs 29.9 months; $P = .8$) and event-free survival (EFS; median, 25.8 months vs 26.7 months; $P = .9$) between the 2 preparative regimens. The increase in CR rate of 11% after the second ASCT observed in our study, among patients who did not reach CR or nCR after the first ASCT, falls within the 2% to 19% response increase with second ASCT reported in tandem autologous transplantation trials[4,5,22,23] and with the double ASCT arm of the 2 studies comparing second ASCT with allo-RIC.[14,15]

There were no significant differences in the prognostic factors at diagnosis between the 2 groups (Table 1). After the second transplantation the CR rate was significantly higher in the allo-RIC group (40% vs 11%; $P = .001$). It should be noted that in our study only patients with suboptimal response (< nCR) to the first ASCT were considered for a second transplantation. The significantly higher CR rate in the allo-RIC group is in line with the Italian experience.[15] In contrast, in the French study no differences in CR rate were observed between second ASCT and allo-RIC.[14] There was a trend toward a higher TRM with allo-RIC (16% vs 5%; $P = .09$). The causes of TRM were 4 bacterial infections in the second ASCT arm and aGVHD (acute graft-versus-host disease; gastrointestinal, 2; liver, 1), and 1 fungal infection in the allo-RIC group. The incidence of grade 2-IV acute GVHD was 32%, and 14 of 21 (66%) patients at risk developed chronic GVHD.

In the present study, with a long follow-up after the second transplantation (median: 5.2 years), there was a trend toward a longer PFS (median, 31 months vs not reached; $P = .08$) in favor of allo-RIC with a plateau for allografting (Figure 1A) and, except for 1 patient who died in CR of chronic GVHD at 4.2 years after transplantation, the remaining 9 patients who achieved CR remain alive in continued CR. However, the EFS (median, 19.6 months vs 26 months; $P = .4$; Figure 1B) and the overall survival (OS; median, 58 months vs not reached; $P = .9$; Figure 1C) were not significantly different between second ASCT and allo-RIC.

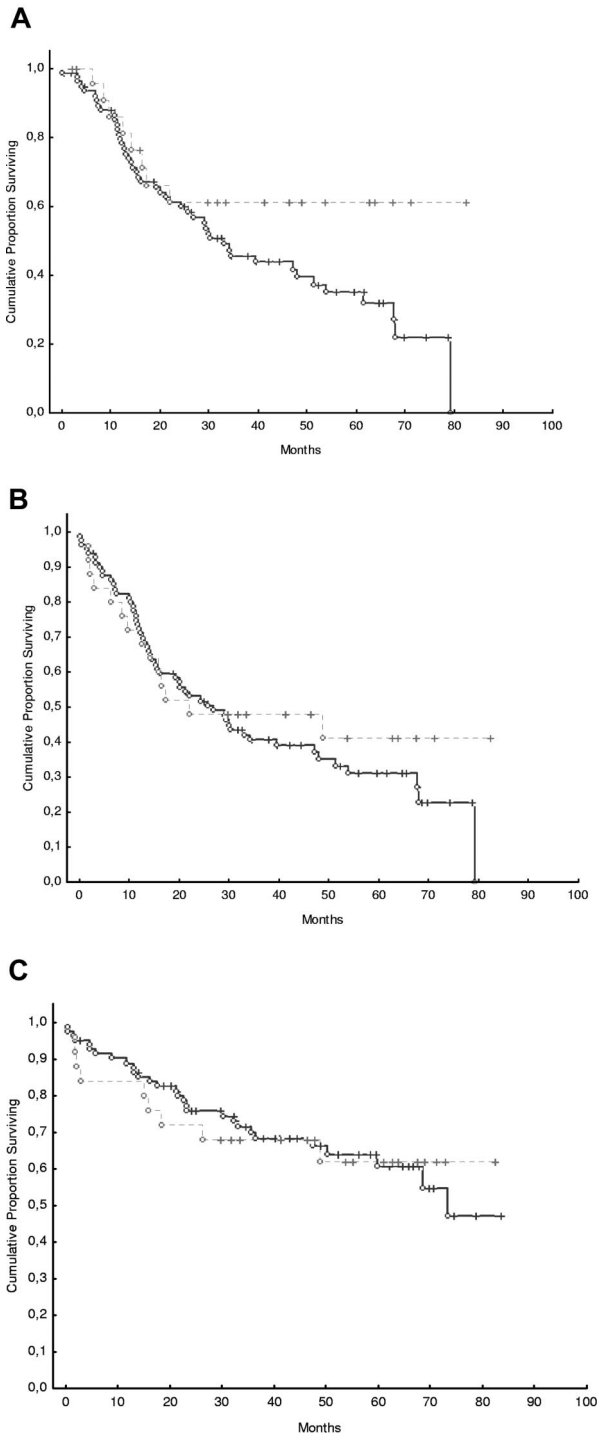

Figure 1. Progression-free, event-free, and overall survival. (A) Progression-free survival (PFS) from second transplantation (median: 31 months for second ASCT and not reached for allo-RIC, $P = .08$; PFS at 5 years with second ASCT and allo-RIC 34.9% [95% CI 22.6%-47.2%] vs 61% [95% CI (confidence interval) 39.8%-82.2%]). (B) Event-free survival (EFS) from second transplantation (median: 26 months for second ASCT and 19.6 months for allo-RIC, $P = .4$; EFS at 5 years with second ASCT and allo-RIC 31% [95% CI 19.4%-42.3%] vs 41% [95% CI 20.2%-62%]). (C) Overall survival (OS) from second transplantation (median: 58 months for second ASCT and not reached for allo-RIC, $P = .9$; OS at 5 years with second ASCT and allo-RIC 60% [95% CI 48.3%-73%] vs 61.8% [95% CI 40.6%-82%]).

The Intergroupe Francophone du Myèlome (IFM) found no differences in EFS and OS when comparing second ASCT with allo-RIC.[14] In contrast, the Italian group reported a significant survival advantage in favor of allo-RIC.[15] Importantly, in the Italian study there was an EFS and an OS plateau beyond 4 years of allografting while there was a continuous relapse rate in the double autograft group. Although in our series there were no significant differences in EFS and OS between double autologous and autograft followed by allo-RIC, there was a trend toward a longer PFS. The different results in these 3 studies can be explained through the different study designs. In the French study only high-risk patients (ie, beta2-microglobulin $>$ 3 mg/L plus 13q-) were included and the conditioning regimen consisted of busulfan/fludarabine/antithymocyte globulin (ATG). In the Italian trial all patients, irrespective of the prognostic factors and the disease status after the first transplantation, were included and the conditioning regimen consisted of 2 Gy total body irradiation.[15] In the present trial, only patients failing to achieve at least nCR with a first ASCT were included and the conditioning regimen was fludarabine/melphalan. Our results are in line with those reported by the Italian group showing lower relapse rate after auto/allo-RIC than after double ASCT, with the presence of a PFS plateau that suggests a curative potential for allografting that relies on the graft-versus-myeloma (GVM) effect. The poor results of French trial could be because only poor-risk patients were included or, alternatively, to the use of T-cell depletion with ATG. Our results indicate that, in patients failing to achieve at least nCR with a first ASCT, a subsequent allo-RIC might be an alternative to a second ASCT because it is associated with a longer PFS. However, because this does not translate to a prolonged EFS and OS, there is a clear need for further improvement in the allo-RIC procedure. Whether or not the incorporation of novel drugs in the allo-transplantation setting will help optimize its efficacy by enhancing the GVM effect while minimizing GVHD remains to be elucidated.[24,25]

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A full list of study participants and institutions can be found on the *Blood* website; see the Supplemental Materials link at the top of the online article.

Authorship

Contribution: L.R. and J.B. reviewed, analyzed, and interpreted the date, performed the statistical analysis, wrote the manuscript, modified subsequent drafts, and finalized the manuscript. J.A.P.-S., A.S., J.J.L., J.d.l.R., and J.S.M. designed the trial and contributed to the analysis and interpretation of the data and to drafting the manuscript. L.R., J.A.P.-S., A.S., J.d.l.R., F.d.A., J.J.L., J.D.G., J.D.-M., B.H., J.G.-F., D.C., A.L., M.H., P.F.A., J.M.B., J.S.M., and J.B. participated in the conception of the study, included patients, provided the PETHEMA database with the patient data and periodic updating, and actively discussed the progress of the trial at the PETHEMA meetings. All the authors reviewed and approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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