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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-Tandem ASCT or ASCT/Allo-RIC in de “novo” MM-

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ABSTRACT

One-hundred and ten patients with multiple myeloma (MM) failing to achieve at least near-complete remission (nCR) after a first autologous stem cell transplant (ASCT) were scheduled to receive a 2nd ASCT (85 patients) or a reduced-intensity-conditioning allograft (Allo-RIC) (25 patients), depending on the HLA-identical sibling donor availability. There was a higher increase in CR rate (40% vs. 11%, p=0.001) and a trend towards a longer progression-free survival (PFS) (median 31 months vs. not reached, p=0.08) in favour of Allo-RIC. In contrast, it was associated with a trend towards a higher transplant-related mortality (16% vs. 5%, p=0.07), a 66% 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 a high morbidity and mortality and, therefore, it should be still considered investigational and restricted to well designed prospective clinical trials. This trial is registered at ClinicalTrials.gov ID number NCT00560053.
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 two randomized trials, double ASCT was superior to a single transplant in patients failing to achieve CR or VGPR after the first transplant (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, the transplant-related mortality (TRM) ranging from 30 to 50% constitutes its major limitation (6-8). The use of dose-reduced intensity conditioning (Allo-RIC) has reduced the TRM to 10-20% (9-15). Interestingly, promising results with autograft followed by an Allo-RIC have been reported (11,13). However, only two 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 nCR after a first ASCT.

PATIENTS AND METHODS

Patients and treatment plan

Patients diagnosed with symptomatic MM from October 1, 1999 to December 31, 2004 who were younger than 70 years were included in the PETHEMA/GEM-2000 trial. They received 6 cycles of VBMCP/VBAD chemotherapy (16) followed by a first ASCT. Patients failing to achieve CR or nCR (i.e., persistence of a serum or urine M-protein on the electrophoretic pattern) were scheduled to receive either a 2nd ASCT conditioned with CVB- cyclophosphamide, etoposide, BCNU- or melphalan-200 or an Allo-RIC conditioned with fludarabine 25 mg/m2 for 5 days and melphalan-70 mg/m2 for 2 days. The treatment assignment to a second autologous transplant 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 CsA and metotrexate.

Out of 752 patients who received a first ASCT, 278 (37%) achieved CR, 124 (16%) nCR, 280 (37%) PR, 45 (6%) SD and 25 (3%) PD. Of the 280 responders failing to achieve CR or nCR, 170 did not undergo the pre-planned second transplant: patient refusal (47), insufficient progenitors (29), PD (27), poor PS (25), physician decision (23), and unknown (19). The remaining 110 patients underwent the planned second transplant: 85 received a 2nd 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 according to 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 assessed according to the EBMT criteria (18), adding the near-CR 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 patients or physician preference, was observed in our series. In patients who underwent a 2nd ASCT, the CR rate for CVB was lower than with MEL-200 (3% vs. 35%, p=0.0004). However, there were no differences in progression-free survival -PFS- (median, 33 vs. 29.9 months; p=0.8) and event-free survival –EFS– (median, 25.8 vs. 26.7 months; p=0.9) between the two preparative regimens. The increase of CR rate in 11% after the 2nd 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 2nd ASCT reported in tandem autologous transplant trials (4,5,22,23) and with the double ASCT arm of the two studies comparing 2nd ASCT with Allo-RIC (14,15).

There were no significant differences in the prognostic factors at diagnosis between the two groups (Table 1). After the second transplant the CR rate was significantly higher in the Allo-RIC group (40% vs. 11%, p=0.001). It should be noted that in our study only patients with suboptimal response (< nCR) to the first ASCT were considered for a second transplant. 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 2nd ASCT and Allo-RIC (14). There was a trend towards a higher TRM with Allo-RIC (16% vs. 5%, p=0.09). The causes of TRM were four bacterial infections in the 2nd ASCT arm and aGvHD (gastrointestinal: 2, liver: 1) and one fungal infection in the Allo-RIC group. The incidence of grade II-IV aGvHD was 32% while 14 of 21 (66%) patients at risk developed cGvHD.

In the present study, with a long follow-up after the second transplant (median: 5.2 years), there was a trend towards a longer PFS (median, 31 months vs. not reached; p=0.08) in favour of Allo-RIC with a plateau for allografting (Figure 1A) and, except one patient who died in CR of cGvHD at 4.2 years post-transplant, all the remaining 9 patients who achieved CR remain alive in continued CR. However, the EFS (median, 19.6 vs. 26 months; p=0.4) (Figure 1B) and the overall survival (OS) (median, 58 months vs. not reached; p=0.9) (Figure 1C) were not significantly different between 2nd ASCT and Allo-RIC.

The French IFM group found no differences in EFS and OS when comparing 2nd ASCT with allo-RIC (14). In contrast, the Italian group reported a significant survival advantage in favour of Allo-RIC (15). Importantly, in the Italian study there was an EFS and OS plateau beyond 4 years of allografting while there was a continuous relapse rate in the double autograft group. Although in our series there are no significant differences in EFS and OS between double autologous and autograft followed by Allo-RIC, there is a trend towards a longer PFS. The different results in these three studies can be explained through the different study design. Thus, in the French study only high-risk patients (i.e., beta2-microglobulin > 3 mg/L plus 13q-) were included and the conditioning regimen consisted of busulfan/fludarabine/ATG. In the Italian trial all patients, irrespective of the prognostic factors and the disease status after the first transplant, were included and the conditioning regimen consisted of 2 Gy TBI (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 which suggests a curative potential for allografting that relies on the graft-versus-myeloma (GvM) effect. The poor results of French trial could be due to the fact that 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 2nd ASCT since it was associated with a longer PFS. However, since this does not translate in 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 contribute to optimize its efficacy by enhancing the GvM effect while minimizing the GvHD remains to be elucidated (24,25).

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For a full list of study participants and institutions, see the online Supplemental Appendix.

AUTHORSHIP CONTRIBUTION STATEMENT
LR and JB reviewed, analyzed and interpreted the date, performed the statistical analysis, wrote the manuscript, modified subsequent drafts and finalized the manuscript. JAPS, AS, JGL, JDL, J de la R, JSM designed the trial, contributed to the analysis, interpretation of the date and to drafting the manuscript. All the authors participated in the conception of the study, included patients, provided the PETHEMA data base with the patients date 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.

The authors report no potential conflicts of interest to this article.
References


LEGEND FOR FIGURE

Figure 1. Panel A: progression-free survival from second transplant (median: 31 months for 2nd ASCT and not reached for Allo-RIC, p=0.08; PFS at 5 years with 2nd ASCT and Allo-RIC 34.9% [95% CI 22.6%-47.2%] vs 61% [95% CI 39.8%-82.2%]). Panel B: event-free survival from second transplant (median: 26 months for 2nd ASCT and 19.6 months for Allo-RIC, p=0.4; EFS at 5 years with 2nd ASCT and Allo-RIC 31% [95% CI 19.4%-42.3%] vs 41% [95% CI 20.2%-62%]). Panel C: overall survival from second transplant (median: 58 months for 2nd ASCT and not reached for Allo-RIC, p=0.9; OS at 5 years with 2nd ASCT and Allo-RIC 60% [95% CI 48.3%-73%] vs 61.8% [95% CI 40.6%-82%]).
Table 1. Characteristics of the patients at diagnosis and response status at second transplant in each group (second auto vs. Allo-RIC)

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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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