Intravenous Busulfan and Melphalan as a Conditioning Regimen for Autologous Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma: A Matched Comparison to a Melphalan-Only Approach

Margarita Blanes1,2, Juan J. Lahuerta3, José D. González4, Paz Ribas5, Carlos Solano6, Adrián Alegre7, Joan Bladé8, Jesús F. San Miguel9, Miguel A. Sanz1, Javier de la Rubia1,10.

Hematology Service, University Hospital La Fe, Valencia, Spain.
Hematology Service, Program of Doctorate of Internal Medicine, Universidad Autónoma de Barcelona, Barcelona, Spain.
Hematology Service, Hospital 12 de Octubre, Madrid, Spain.
Hematology Service, Hospital Insular de Canarias, Las Palmas, Spain.
Hematology Service, Hospital Dr. Peset, Valencia, Spain.
Hematology Service, Hospital Clínico, Valencia, Spain.
Hematology Service, Hospital Universitario de la Princesa, Madrid, Spain.
Hematology Service, Hospital Universitario de Salamanca, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.
Hematology Service, Hospital Universitario de Salamanca, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.
Hematology Service, Hospital Universitario de Salamanca, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.
Hematology Service, Hospital Universitario de Salamanca, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.
Hematology Service, Hospital Universitario de Salamanca, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.

ABSTRACT
Melphalan 200 mg/m² (MEL200) is the standard conditioning regimen administered to newly diagnosed patients with multiple myeloma (MM) undergoing autologous stem cell transplantation (ASCT). Few alternatives have been explored in order to improve the antimyeloma activity of this conditioning. We compare i.v. busulfan (BU) 9.6 mg/kg and MEL 140 mg/m² (MEL140) versus MEL200 mg/m² as a conditioning regimen before ASCT for newly diagnosed patients with MM. For this purpose, 51 patients receiving i.v. BU plus MEL were compared to 102 patients receiving MEL200 mg/m² in a 1:2 matched control analysis. Matching criteria included age, clinical stage at diagnosis, and response to induction therapy. No differences in the overall and complete response (CR) rates were observed after ASCT between both groups. After a median follow-up of 63 and 50 months in control and BU plus MEL groups, progression-free survival (PFS) was 24 and 33 months, respectively (P = .10). Most frequent toxicities included mucositis and febrile neutropenia in both groups. No case of sinusoidal obstruction syndrome was observed. Transplant-related mortality was 4% and 2% in BU plus MEL and control groups, respectively. ASCT conditioned with i.v. BU plus MEL may be considered an effective and well-tolerated alternative to a MEL-only approach as a conditioning regimen for patients with MM who are candidates for ASCT. (Clinicaltrial.gov identifier: NCT00560053 and NCT00804947.)

© 2013 American Society for Blood and Marrow Transplantation.

INTRODUCTION
Autologous stem cell transplantation (ASCT) is considered the standard of care for patients younger than 65 years with newly diagnosed multiple myeloma (MM) [1-5], based on the results of a randomized trial of the Intergroup Francophone du Myeloma [6], showing that melphalan 200 mg/m² (MEL200) was superior to MEL140 plus total body irradiation (TBI). In spite of the theoretical clinical relevance of the conditioning regimen, progress in this area is relatively scarce. Moreover, most of the alternative preparative regimens that so far have been investigated did not show convincing evidence of superiority over MEL200 [7-16]. Nevertheless, the interest in the field may be renewed with the availability of novel antimyeloma effects.

Results of 2 retrospective studies conducted by the Programa Español de Tratamientos en Hematología/Grupo Español de Mieloma (PETHEMA/GEM) study groups showed encouraging results in terms of response rate and progression-free survival (PFS) with the combination of oral busulfan (BU) and MEL compared with MEL200 or MEL140 mg/m² (MEL140) plus TBI [17,18]. Based on these results, PETHEMA/GEM launched a prospective trial (PETHEMA/GEM2000) aimed to investigate the combination of oral BU and MEL (BUMEL) as a conditioning regimen in patients with newly diagnosed MM. The first interim analysis of this trial showed a higher than expected hepatic toxicity, particularly sinusoidal obstructive syndrome (SOS) [19], and the protocol was amended so that MEL200 became the preparative regimen. However, and despite this complication, final results of this study with a longer follow-up showed that conditioning with BUMEL was associated with a longer PFS than that observed with MEL200 [20].

Taking advantage of the availability of an i.v. formulation of BU, we conducted a phase II, prospective, multicenter trial of i.v. BUMEL as a preparative regimen in a series of 55 patients with MM undergoing ASCT either as front-line therapy or after relapse from a previous transplantation. Our results showed that BUMEL was associated with a high response-rate and a low transplant-related mortality [21].
Based on these encouraging results, we have now performed a matched case-control analysis to compare the outcome of patients with MM undergoing front-line therapy and a single ASCT after i.v. BUMEL or MEL200 as a preparative regimen.

MATERIALS AND METHODS

BUMEL Group

Between June 2005 and September 2009, a series of 51 consecutive patients with newly diagnosed MM from 5 institutions participating in the BUMEL phase II trial were included in the study [21]. Induction therapy consisted of 6 cycles of vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP), alternating with vincristine, carmustine, adriamycin, and dexamethasone (VBAD) or vincristine, adriamycin, and dexamethasone followed by ASCT prepared with i.v. BUMEL.

Control Group

For comparison, 102 pair mates were selected as the control group among patients who entered the GEM2000 study in a 2:1 ratio. The GEM2000 protocol was active from January 2000 to February 2005. For patients included in this study, induction therapy was similar to that administered to the BUMEL group of patients, but this was followed by ASCT prepared with MEL200. Patients failing to achieve complete response (CR) or near CR (nCR) after ASCT were offered as a second autologous transplantation [22–26].

Matched Control Study Details

Case matching was performed according to age, clinical stage at diagnosis (Durie-Salmon and International Staging System), and response to induction therapy. To ensure a homogeneous selection of patients in the control group, and in order to minimize the risk of bias (selecting an unusual proportion of CR/nCR after transplantation in this group), those patients receiving 2 autologous transplantsations were potentially eligible during the matching process.

In both studies, informed consent was provided according to the Declaration of Helsinki. The GEM2000 protocol and BUMEL clinical trial were registered at ClinicalTrials.gov as NCT00560053 and NCT00804947, respectively.

Autologous Transplantation

The BUMEL conditioning regimen consisted of BU at a dose of 3.2 mg/kg administered i.v. over 3 hours once on a day on days 5 to 3 (total dose 9.6 mg/kg), followed by MEL at a dose of 140 mg/m² on day 2. Patients included in the control group underwent ASCT after being conditioned with MEL200 mg/m² in a single dose on day –2 or in 2 divided doses on days –3 and –2. As it has been previously mentioned, patients failing to achieve at least nCR were offered a second autologous transplantation. The preparative regimen in this second transplantation was either MEL200 or a combination of cyclophosphamide (1.5 mg/kg/d, days –6 to –3), carmustine (300 mg/m², day –6), and etoposide (125 mg/m²/12 h, days –6 to –4). The minimum threshold dose of CD34+ cells to be collected in the control group was 4 × 10⁶ per kilogram of body weight, and the minimum number of CD34+ cells to undergo transplantation in the BUMEL group was 2 × 10⁶ per kilogram of body weight. All patients received supportive care measures, including growth factor support, blood transfusions, and prophylactic or therapeutic antibiotics according to local departmental guidelines at the time. In addition, every patient in the BUMEL group received oral phenytoin for seizure prophylaxis. Finally, maintenance treatment with α-interferon and steroids was given in 65 patients (64%) in the control group, whereas 33 of the 51 patients (65%) in the BUMEL group received maintenance that consisted of α-interferon and steroids (29 patients) or immunomodulatory agents (4 patients).

Definitions

Disease status at transplantation and the response to ASCT was evaluated according to the European Group for Blood and Marrow Transplantation criteria, but an nCR category, as defined by disappearance of monoclonal protein at routine electrophoresis but positive immunofixation, was added to European Group for Blood and Marrow Transplantation criteria [2,27]. Responses were assessed at the time of enrollment (after induction therapy) and 3 months after ASCT. Toxicities were graded according to criteria reported by Bearman et al. [28]. Duration of hospitalization was measured from the day of transplantation to the day of discharge, and any death unrelated to relapse or disease progression during the first 100 days was considered an event for transplant-related mortality.

Statistical Analysis

The primary objective of this study was to compare the overall response and CR/nCR rate 3 months after ASCT. Secondary endpoints were safety profile of the conditioning regimens, PFS, time to progression (TTP), and overall survival (OS). The proportions of patients with a given set of characteristics were compared by the chi-square test or by the Fisher exact test. Differences in the means of continuous measurements were tested by the t test and checked by the Mann-Whitney U test. The duration of PFS was calculated for all patients from the day of transplantation to the TTP, relapse, death from any cause, or reference date. TTP was estimated from the day of transplantation to the date of relapse or disease progression and OS from the day of transplantation to the date of death or the last visit. PFS, TTP, and OS were plotted according to the Kaplan-Meier product-limit method with comparisons made by the log-rank test. All patients were followed until death or reference date (March 31, 2012). All statistical analyses were performed with BMDP software (BMDP, University of California, Berkeley, CA).

RESULTS

Patient Characteristics

A summary of patient characteristics and laboratory parameters are given in Table 1. As per protocol, patients in both groups had similar disease characteristics at diagnosis and comparable response status before transplantation. VBMCP/VBAD chemotherapy was administered to 42 patients (82%) and 99 patients (97%) in the BUMEL and control groups, respectively. Median time between diagnosis and transplantation was 9.2 months (range, 5–13.1 months) and 9.4 (range, 4.2–14.7 months) in the BUMEL and control groups, respectively. Finally, in the control group, and according to the protocol design, 19 patients who did not achieve CR with this first transplantation underwent a second transplantation within 8 months after the first ASCT.

Engraftment and Transplant-related Complications

The hematopoietic reconstitution was similar in the 2 groups. The median time to reach a neutrophil count >0.5 × 10⁹/L was 11 days in both groups. The median time to reach a platelet count greater than 20 × 10⁹/L was 13 days in the BUMEL group and 12 days in the control group (Table 2).

Regimen-related toxicities are detailed in Table 2. Mucositis was the nonhematologic toxicity most frequently observed in both groups (45 and 47 patients in the BUMEL and control group, respectively) followed by febrile neutropenia, 43 patients (16 bacteremias) in the BUMEL and 62 patients (24 bacteremias) in the control group. Hepatic toxicity was not reported in the control group, whereas mild (grade I/II) liver toxicity was observed in 7 patients (14%) among BUMEL recipients, although no patient developed SOS. Other toxicities observed during the early post-transplantation period are shown in Table 2. Overall, the median duration of hospitalization was 21 and 17 days in the BUMEL and control group, respectively (P = 0.04) (Table 2).

Finally, there were 2 (4%) treatment-related deaths in the BUMEL group and 2 (2%) in the control group. Three of the 4 patients died because of infectious complications, and the remaining patient died due to a sudden cardiac arrest 22 days after transplantation (Table 2).

Response after ASCT

The response rate after ASCT is shown in Table 3. No differences in the overall response and in the CR/nCR were observed between both groups of patients. The overall response rate was 90% and 91% in the BUMEL and in the control group, respectively. Twenty-three patients (45%) improved their response after transplantation in the BUMEL group, with 26 patients (51%) achieving either CR (23.5%) or nCR (27.5%) and 20 (39%) had a partial response (PR), whereas in the control group, 34 patients (33%) achieved CR, 16 patients (16%) achieved nCR, and 43 patients (42%) had a PR.
Survival Analysis

**PFS**

After a median follow-up of 50 and 63 months, 30 patients had relapsed in the BUMEL group and 82 patients in the control group with a median PFS of 33 months for those receiving BUMEL and 24 months for patients in the control group (33 versus 24 months and 37 versus 26 months, respectively). PFS and TTP was, however, longer among patients receiving BUMEL when compared with those receiving a MEL-only conditioning regimen (33 versus 24 months and 37 versus 26 months, respectively), with a PFS at 6 years of 23% and 17% in the BUMEL and control group, respectively.

**TTP**

Median TTP was 37 months (95% CI, 31% to 43%) and 26 months (95% CI, 23% to 29%) in BUMEL and MEL200, respectively (P = .10; Figure 2).

**OS**

At the time of this analysis, 24 patients (47%) have died in the BUMEL group. Twenty-one were myeloma-related deaths, 2 patients died because of transplant-related mortality, and the remaining patient died because of an acute myocardial infarction 56 months after transplantation. Overall, 62 patients (61%) have died in the control group: 53 because of relapse or progression and 5 because of transplant-related complications (2 patients died after the first transplantation and 3 after the second transplantation), and 4 patients died while in response between 16 and 55 months after transplantation because of septic shock (1 patient), acute myocardial infarction (1 patient), and of unknown cause in the remaining 2 patients. The median OS was 65.5 months for patients receiving BUMEL and 63 months for those in the control group (P = .86; Figure 3).

**DISCUSSION**

In the present study, we compared the clinical outcomes of a series of 51 patients with newly diagnosed MM who underwent transplantation after BUMEL conditioning to that of double the number of matched patients who received MEL200 only. Our results show a similar overall response and CR/nCR rate in both groups of patients. PFS and TTP was, however, longer among patients receiving BUMEL when compared with those receiving a MEL-only conditioning regimen (33 versus 24 months and 37 versus 26 months, respectively), with a PFS at 6 years of 23% and 17% in the BUMEL and control group, respectively.

---

**Table 1**

Characteristics of Patients According to Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BUMEL group (n = 51)</th>
<th>Control group (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>61</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (47-70)</td>
<td>61 (40-71)</td>
</tr>
<tr>
<td>Durie-Salmon stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>III</td>
<td>29</td>
<td>57</td>
</tr>
<tr>
<td>ISS stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Isotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>IgA</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Light chain</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.9 (4.9-15)</td>
<td>10.8 (4-15)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1 (0.54-8.8)</td>
<td>1 (0.4-9)</td>
</tr>
<tr>
<td>β-2 microglobulin (mg/L)</td>
<td>3.6 (1.3-17.6)</td>
<td>3.2 (0.5-24.2)</td>
</tr>
<tr>
<td>Chemotherapy before ASCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VBMCP/VBAD</td>
<td>42</td>
<td>82</td>
</tr>
<tr>
<td>VAD</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Interval Dx-ASCT (months)</td>
<td>9.2 (5.1-13.1)</td>
<td>9.4 (4.2-14.7)</td>
</tr>
</tbody>
</table>

BUMEL indicates busulfan and melphalan; ISS, International Staging System; ASCT, autologous stem cell transplant; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VBAD, vincristine, carmustine, adriamycin, and dexamethasone; VAD, vincristine, adriamycin, and dexamethasone; Dx, diagnosis.

Note: No statistically significant differences were found between the 2 treatment groups.

- BUMEL group: IgG (2 patients); IgM (1 patient); nonsecretory (3 patients); Control group: nonsecretory (2 patients).

---

**Table 2**

Engraftment and Transplant-Related Toxicities According to Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BUMEL group (n = 51)</th>
<th>Control group (n = 102)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMN &gt;0.5 × 10^9/L, days (range)</td>
<td>11 (9-33)</td>
<td>11 (7-22)</td>
<td></td>
</tr>
<tr>
<td>Platelet &gt;20 × 10^9/L, days (range)</td>
<td>13 (9-64)</td>
<td>12 (6-63)</td>
<td>.66</td>
</tr>
<tr>
<td>Hospitalization, days (range)</td>
<td>21 (12-42)</td>
<td>17 (11-41)</td>
<td>.04</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>43 (84)</td>
<td>62 (61)</td>
<td>.01</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>19 (37)</td>
<td>24 (23.5)</td>
<td></td>
</tr>
<tr>
<td>MDI/bacteremia</td>
<td>16 (31)/16 (31)</td>
<td>28 (27)/24 (23.5)</td>
<td>.0001</td>
</tr>
<tr>
<td>CDI</td>
<td>8 (16)</td>
<td>10 (10)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>45 (88)</td>
<td>47 (46)</td>
<td>.0001</td>
</tr>
<tr>
<td>Grade I/II</td>
<td>10/35</td>
<td>14/33</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8 (16)</td>
<td>13 (13)</td>
<td></td>
</tr>
<tr>
<td>Grade I/II</td>
<td>10/33</td>
<td>10/33</td>
<td></td>
</tr>
<tr>
<td>Transplant-related mortality</td>
<td>2/4*</td>
<td>2/2*</td>
<td></td>
</tr>
</tbody>
</table>

BUMEL indicates busulfan and melphalan; PMN, neutrophil; MDI, microbiological documented infection; CDI, clinically documented infection. Values are number (%) of patients.

- BUMEL group: cardiac toxicity, 1 patient. Control group: cardiac toxicity, 2 patients; renal toxicity, 1 patient; pulmonary toxicity, 1 patient; central nervous system toxicity, 1 patient.
- Pneumonia and septic shock by Klebsiella pneumoniae (1 patient) and septic shock by Acinetobacter spp (1 patient).
- Septic shock (1 patient) and sudden cardiac arrest (1 patient).

---

**Table 3**

Response before and after ASCT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BUMEL group (n = 51)</th>
<th>Control group (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ASCT</td>
<td>After ASCT</td>
<td>Before ASCT</td>
</tr>
<tr>
<td>CR</td>
<td>4 (8)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>nCR</td>
<td>6 (12)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>PR</td>
<td>32 (62)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>MR</td>
<td>5 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

BUMEL indicates busulfan and melphalan; ASCT, autologous stem cell transplant; CR, complete response; nCR, near complete response; PR, partial response; MR, minimum response; SD, stable disease; PD, progressive disease.

Values are number (%) of patients.
Appreciating the difficulty of drawing firm conclusions from historic controls, an effort was undertaken to account for differences in relevant prognostic features by matching patients closely for age, clinical stage, and response to induction therapy. The primary endpoint of the study was to compare overall response and CR/nCR rate in both groups of patients. Our results show a similar overall response and CR/nCR rate with BUMEL (90% and 51%) to that observed with MEL200 (91% and 49%). Furthermore, CR/nCR in the BUMEL group mirrored the previous PETHEMA/GEM experience, confirming the i.v. formulation of BU as having similar clinical efficacy than the oral one [19].

Notwithstanding the similar response rate, TTP (37 versus 26 months) and PFS (33 versus 24 months) were longer in the BUMEL group of patients despite the fact that 19 patients in the MEL200 group underwent a second ASCT. A prolonged PFS with an equivalent CR/nCR rate posttransplantation has also been reported in a recent update of results of the GEM2000 trial (41 versus 31 months for patients treated with oral BUMEL and MEL200, respectively; \(P = .009\)) [20], adding further evidence of the high antmyeloma activity of the BUMEL combination as a preparative regimen for ASCT. As in the previous PETHEMA/GEM2000 study, our results also showed a longer PFS both when considering patients achieving CR/nCR or less than nCR after transplantation (data not shown). This finding could be because of a better quality of response (more profound cytoreduction) obtained with BUMEL than with MEL200. Unfortunately, only conventional methods were used to evaluate response after transplantation. Thus, further studies including more sensitive methods to assess response are needed to confirm this hypothesis [26,29,30]. Finally, although formal comparisons are not possible between different studies, our results show that duration of PFS achieved with BUMEL conditioning regimen compares favorably with other series performing single transplantation with MEL200 as the preparative regimen (21-30.6 months) [3,6,31,32] and is similar to trials including a double tandem transplantation approach with MEL-only preparative regimens [33–35].

Diagnostic cytogenetic abnormalities in MM have been associated with the outcome [36]. However, cytogenetic was not a standard diagnostic procedure at the time when the GEM2000 (control group) trial was launched and many patients did not have this information available. Thus, we could not match patients according to this important prognostic factor.

Hematopoietic recovery was similar in both groups of patients and within the limits expected in patients undergoing autografting with peripheral blood stem cells and the procedure was well-tolerated with a low transplant-related mortality. Mucositis was the most commonly reported toxicity, it was more frequently observed among BUMEL recipients, and it was associated with a longer duration of hospitalization in this group of patients (21 versus 17 days). Febrile neutropenia was more frequently observed among those receiving BUMEL (84% versus 61%), although there

---

**Figure 1.** Progression free survival in BUMEL group (—) and control group (⋯).

**Figure 2.** Time to progression in BUMEL group (—) and control group (⋯).
were no differences in the incidence of microbiologically documented infections between both groups. Seven of the 51 patients (14%) conditioned with BUMEL developed grade I/II liver toxicity that did not require any specific therapy. Interestingly, however, no patient developed hepatic SOS. This finding, probably due to the absence of a first-pass hepatic effect of i.v. BU, supports our previous experience [21] and that reported by other authors [37] as well as confirms the higher safety profile of the i.v. formulation of BU compared with the oral counterpart.

A conditioning regimen with bortezomib and MEL has also been recently evaluated in patients with newly diagnosed MM undergoing ASCT with encouraging results [38]. Although MEL200 should still be considered the standard condition regimen for ASCT in MM, based on our data and data from literature, it is reasonable to design randomized studies comparing MEL200 with i.v. BUMEL to optimize the outcomes of ASCT in patients with MM as part of upfront strategy therapy and to determine if i.v. BUMEL offers an advantage over MEL200 alone.

ACKNOWLEDGMENTS

Financial disclosure: All authors declared no conflicts of interest.

Authorship Statement: JR, MB, JL, JS, JB, and MS designed and performed the trial; MB, JL, JC, PR, CS, AA, JB, JS, MS, and JR contributed to collect data; JR and MB analyzed and interpreted data, performed statistical analysis, and wrote the manuscript. All authors reviewed and approved the manuscript.

This study was supported in part by research funding from grants “Red Temática de Investigación Cooperativa en Cancer” RD06/0020/0031 and RD06/0020/0005 and “Red de Biobancos Hospitalarios” RD09/0076/00021, research project PS09/01882 from the “Instituto de Salud Carlos III”, research grant CA08/00141, CM10/00321 and CM09/00038 from the “Instituto de Salud Carlos III”, and “Ministerio de Ciencia e Innovación” grant BES2008-008053.

REFERENCES


22. Gutierrez NC, Castellanos MV, Martin ML, et al. Prognostic and biological implications of genetic abnormalities in multiple myeloma undergoing autologous stem cell transplantation: t(4;14) is the most relevant adverse prognostic factor, whereas RB deletion as a unique abnormality is not associated with adverse prognosis. *Leukemia*. 2007;21:143-150.


