

Busulfan 12 mg/kg plus melphalan 140 mg/m² versus melphalan 200 mg/m² as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study

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ABSTRACT

Background

The aim of this study was to compare the long-term safety and efficacy of oral busulfan 12 mg/kg plus melphalan 140 mg/m² and melphalan 200 mg/m² as conditioning regimens for autologous stem cell transplantation in newly diagnosed patients with multiple myeloma in the GEM2000 study.

Design and Methods

The first 225 patients received oral busulfan 12 mg/kg plus melphalan 140 mg/m²; because of a high frequency of veno-occlusive disease, the protocol was amended and a further 542 patients received melphalan 200 mg/m².

Results

Engraftment and hospitalization times were similar in both groups. Oral busulfan 12 mg/kg plus melphalan 140 mg/m² resulted in higher transplant-related mortality (8.4% versus 3.5%; $P=0.002$) due to the increased frequency of veno-occlusive disease in this group. Response rates were similar in both arms. With respective median follow-ups of 72 and 47 months, the median progression-free survival was significantly longer with busulfan plus melphalan (41 versus 31 months; $P=0.009$), although survival was similar to that in the melphalan 200 mg/m² group. However, access to novel agents as salvage therapy after relapse/progression was significantly lower for patients receiving busulfan plus melphalan (43%) than for those receiving melphalan 200 mg/m² (58%; $P=0.01$).

Conclusions

Conditioning with oral busulfan 12 mg/kg plus melphalan 140 mg/m² was associated with longer progression-free survival but equivalent survival to that achieved with melphalan 200 mg/m² but this should be counterbalanced against the higher frequency of veno-occlusive disease-related deaths. This latter fact together with the limited access to novel salvage therapies in patients conditioned with oral busulfan 12 mg/kg plus melphalan 140 mg/m² may explain the absence of a survival difference. Oral busulfan was used in the present study; use of the intravenous formulation may reduce toxicity and result in greater efficacy, and warrants further investigation in myeloma patients. (*Clinicaltrials.gov identifier: NCT00560053*).

Key words: multiple myeloma, melphalan, oral busulfan, conditioning regimens, autologous stem cell transplantation, survival, progression-free survival.

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Introduction

In multiple myeloma (MM) patients, the use of high-dose chemotherapy supported by autologous stem cell transplantation (HDT/SCT) has led to improvements in response rate, progression-free survival, and, in some studies, overall survival compared with the outcomes achieved with conventional chemotherapy.^{1,2} Although this treatment approach has been used for over 20 years,^{3,4} having become the standard of care for patients under the age of 65–70 years,^{5,6} research focused on improving the anti-myeloma efficacy of HDT has been scarce.

After initial cases described by McElwain and Powles,³ the first standard HDT regimen with SCT support was reported by the Arkansas Group in 1987, and consisted of total body irradiation with 850 cGy followed by intravenous melphalan 140 mg/m² (MEL140).⁷ The second and most widely accepted regimen was reported in 1992 by the same group⁸ and was based on a single dose of melphalan 200 mg/m² (MEL200). The *Intergroupe Francophone du Myélome* (IFM) 9502 randomized trial compared both regimens and established the latter as the universal standard conditioning regimen, on the basis that MEL200 was less toxic and was associated with a trend towards longer overall survival than MEL140 plus total body irradiation.⁹

The IFM also explored the value of increasing the dose of melphalan to 220 mg/m² for high-risk MM patients but this resulted in excessive gastrointestinal toxicity and further evaluation was abandoned.^{10,11} Likewise, other HDT regimens, including busulfan alone,¹² busulfan plus either cyclophosphamide¹³ or melphalan,¹⁴ or combinations of other drugs^{15,16} have not progressed into full clinical development. More recently, novel drugs, such as bortezomib, have been incorporated into the conditioning regimens, but without consolidated results yet.^{17,18}

Nevertheless, some of these HDT regimens may have potential. Our group published the results of two retrospective studies^{19,20} in which the use of oral busulfan 12 mg/kg plus MEL140 (BUMEL) resulted in a longer median progression-free survival (30 months) compared with MEL200 (22 months) or MEL140 plus total body irradiation (20 months). Thus, the *Programa Español de Tratamientos en Hematología* (PETHEMA)/ *Grupo Español de Mieloma* (GEM) decided to prospectively investigate the BUMEL conditioning regimen in patients with newly diagnosed MM in the GEM2000 protocol. However, the first interim analysis²¹ revealed a high incidence of hepatic veno-occlusive disease (VOD) and the protocol was amended so that MEL200 became the conditioning treatment.

Here we report the final results of the prospective, non-randomized GEM2000 study with particular focus on the impact of receiving either BUMEL or MEL200 conditioning. The only difference between the two groups was the date of study entry; inclusion criteria, initial induction regimen (VBMCP/VBAD), interval from diagnosis to transplant, and planned post-transplant therapy remained identical across both groups.

Design and Methods

Therapeutic program

As outlined previously,^{22–26} the GEM2000 protocol was active from January 2000 to February 2005 (ClinicalTrials.gov:

NCT00560053); patients aged less than 70 years with symptomatic, newly diagnosed MM who were candidates for HDT/SCT were included. Patients received induction therapy comprising six alternating cycles of VBMCP/VBAD chemotherapy, with peripheral blood stem cell collection after cycle 4 using granulocyte colony-stimulating factor 16–24 µg/kg daily for 5 days for priming. After peripheral blood stem cell collection (target $\geq 2 \times 10^6$ CD34⁺ cells/kg) and two additional cycles of VBMCP/VBAD, patients underwent their first HDT/SCT.²⁷ Patients failing to achieve complete response or near complete response were offered either a tandem autologous transplant or a reduced-intensity conditioning allogeneic transplant if a human leukocyte antigen (HLA)-identical sibling donor was available. Following HDT/SCT (either single or tandem), all patients were scheduled to receive 2 years maintenance therapy with interferon (3 MU three times weekly) and prednisone (50 mg on alternate days). The protocol was approved by the local research ethics committees of all participating institutions; all patients provided written informed consent. This study is registered at ClinicalTrials.gov as NCT00560053.

Myeloablative therapy

The first 225 patients included in the trial received BUMEL (oral busulfan 1 mg/kg every 8 h on days –6 to –3 [total dose 12mg/kg], plus melphalan 140 mg/m² in a single dose on day –2) as conditioning. Following results of the interim analysis performed in June 2002 showing a high incidence of VOD (8%) and a transplant-related mortality of 8.4%²¹ BUMEL was stopped and the protocol was amended from BUMEL to MEL200 as conditioning (melphalan 200 mg/m² in a single dose on day –2 or in two divided doses on days –3 and –2).

Patients

One thousand and seventy-five consecutive patients were enrolled in GEM2000. One hundred and seventeen (11%) of those pre-selected were excluded for failing to meet inclusion criteria (non-secretory MM, age > 75 years, serum creatinine > 2 mg/dL, or relevant comorbidities). Another 173 (16%) patients who started chemotherapy did not proceed to transplantation due to progressive disease followed by death or protocol change (n=68), serious comorbidity (n=34), patients' decision (n=31), failure of peripheral blood stem cell mobilization (n=30), and other reasons (n=13). Of the 782 patients eventually transplanted, nine were excluded from the final analysis because SCT was performed with bone marrow (n=1), bone marrow plus peripheral blood stem cells (n= 1) or purged peripheral blood stem cells (n= 7); other cases could not be evaluated (n=7) because of insufficient or inconsistent data. Therefore, for this study 767 patients were evaluable: 225 treated with BUMEL and 542 with MEL200.

End-points

Time to granulocyte recovery was defined as the number of days from infusion until a neutrophil count of greater than $0.5 \times 10^9/L$ was reached. Time to platelet recovery was defined as the number of days from infusion to the first of 7 consecutive days with a platelet count greater than $20 \times 10^9/L$. The time between peripheral blood stem cell infusion and discharge was considered the hospitalization time. Transplantation-related mortality was defined as any death occurring within 100 days after infusion of the peripheral blood stem cells (limit not applied in cases of VOD because of the singularly late onset of this complication),²¹ excluding those deaths that could be directly attributed to disease progression. Toxicity was recorded according to the Seattle regimen-related toxicity grading²⁸ and the diagnosis of VOD was established using both the Seattle²⁹ and Baltimore³⁰ criteria.

Disease response was assessed post-induction and 90 days post-

transplant using European Group for Blood and Marrow Transplantation (EBMT) criteria,³¹ modified to include near complete response. The reference M-protein level for each patient was that recorded at initiation of induction therapy.

In each conditioning group, overall survival and progression-free survival were assessed from the time of transplantation. Progression-free survival was measured until progression, relapse, or death. Patients who had not progressed or relapsed were censored on the last date they were known to be alive and event-free. Overall survival was calculated until date of death or last visit.

Statistical analysis

All statistical analyses were performed using Statistica 7.0 software (StatSoft Inc., Tulsa, OK, USA). For univariate analysis, survival curves were calculated according to the Kaplan-Meier method and differences were evaluated using a log-rank test. *P* values less than 0.05 were considered to indicate a statistically significant difference. Multivariate analysis was performed using an adjusted Cox proportional-hazards regression model. After stepwise regression analysis (all prognostic factors shown in Table 1 were initially included), the variables selected for the progression-free survival model were: hemoglobin of 10 g/dL or less, International Staging System (ISS) disease stage,³² pre- and post-HDT/SCT response status (χ^2 *P* from 0.0002 to $<10^{-6}$); for the overall survival model, the variables selected were hemoglobin of 10g/dL or less, Eastern Cooperative Oncology Group performance status at diagnosis, lactate dehydrogenase above the normal limit,

and pre-/post-HDT/ASCT response status (χ^2 *P* from 0.002 to $<10^{-6}$). The χ^2 and Fisher's exact two-sided tests were used for comparisons between categorical variables and the Wilcoxon rank-sum or *t*-test was used for continuous variables.

Results

Patients

The flow of patients through the study protocol is shown in Figure 1. In total, 767 patients received at least one HDT/SCT and were included in this analysis: 225 received BUMEL and 542 received MEL200 conditioning. Overall, 332 patients achieved either partial response, minor response or stable disease after their first HDT/SCT and, per protocol, were candidates for a second transplant; however, 190 did not proceed, mainly due to the patients' refusal. The median follow-up was 48 months.

Patients in both conditioning groups had similar disease characteristics at diagnosis (Table 1). In the BUMEL group, patients were slightly younger (median age 56 *versus* 58 years, *P*=0.002), and the frequency of patients who underwent tandem transplantation was higher (54 *versus* 35%, *P*=0.001) than in the MEL200 group. As shown in Table 1, times from diagnosis to SCT and response status before HDT/SCT were not significantly different between groups.

Table 1. Characteristics of patients at diagnosis, tandem transplantation frequency and disease status prior to transplantation according to conditioning regimen.

	BUMEL N=225 At diagnosis	MEL200 N=542 At diagnosis
Sex (male), %	46	45
Age, years	56 (55–57, ± 8)	58 (57–59, ± 8)*
M-protein (IgG/ IgA/ light chain), %	52/ 26/ 22	56/ 27/ 17
Performance status (ECOG), $<2/2$, %	58/ 42	58/ 42
ISS Stage I / II / III, %	37/ 43/ 20	34/ 48/ 18
Time from diagnosis to ASCT, months	9.5 (9.2–9.7 ± 2.1)	9.8 (9.6–10 ± 2.6)
CD34 ⁺ cells/kg infused	3.1 (2.9–3.4 ± 1.7)	3.05 (2.9–3.1 ± 1.5)
Tandem transplantation in non-nCR/CR patients, %	54	35*

	At diagnosis	At transplantation	At diagnosis	At transplantation
Creatinine, mg/dL	1.2 (1.1–1.4, ± 1)	0.8 (0.8–0.9, ± 0.3)	1.2 (1.1–1.3, ± 0.8)	0.9 (0.9–1, ± 0.6)
Albumin, g/dL	3.7 (3.4–3.9, ± 1.7)	3.7 (3.6–3.8, ± 0.5)	3.6 (3.4–3.7, ± 1.6)	4 (3.8–4.2, ± 2.6)
Albumin ≥ 3.5 g/dL	55	71	55	75
Calcium, mg/dL	9.8 (9.6–10.1, ± 1.7)	9 (8.9–9.1, ± 0.8)	9.8 (9.5–10.2, ± 1.8)	9 (8.9–9.1, ± 0.8)
Calcium, >10 mg/dL	35	7	29	8
Hemoglobin, g/dL	10.5 (10.2–10.8, ± 2.3)	11.6 (11.4–11.8, ± 1.5)	11.1 (10.8–11.1, ± 2.1)*	12 (11.9–12.1, ± 1.5)
Hemoglobin, ≤ 10 g/dL	41	12	33	7
β_2 microglobulin, mg/L	3.4 (3.1–3.7, ± 1.9)	2.3 (2.1–2.5, ± 1.3)	3.4 (3.2–3.5, ± 1.9)	2.3 (2.2–2.4, ± 1.1)
β_2 microglobulin ≥ 3.5 mg/L	34	11	32	12
LDH $>$ normal limit	12	12	13	12
Response status pre-HDT/SCT:				
PD/ SD/ PR	-	4.8/ 13.7/ 55	-	4.7/ 13/ 57.7
Response status pre-HDT/SCT: nCR/ CR	-	13.7/ 12.8	-	12/ 12.6

Mean values (CI 95%, \pm SD) are given for continuous variables, or percentage of patients with that characteristic. *Statistically significant differences. BUMEL: 12 mg/kg, plus melphalan at 140 mg/m²; MEL200 200 mg/m² melphalan. HDT/SCT: high dose chemotherapy and stem cell support; ISS: International Staging System; ASCT: autologous stem cell transplantation; nCR: near complete response; CR: complete response; PD: progressive disease; SD: stable disease; PR: partial response; LDH: lactate dehydrogenase.

Hematologic recovery and hospitalization time

The number of CD34+ cells infused did not differ between the two conditioning groups (Table 1); no cases of graft failure were reported. In patients receiving growth factors (BUMEL 91%, MEL200 94%), no differences were observed between the BUMEL and MEL200 groups in mean time to granulocyte recovery (11.6, [95% confidence interval (CI): 11.1–12.1±3.4] versus 11.8 [11.5–12±2.9] days; *P*=0.4), mean time to platelet engraftment (14.0 [12.2–15.8±12.7] versus 16.2 [13.7–18.8±29.2] days; *P*=0.2), or mean hospitalization time (19.7 [18.5–20.9±8.2] versus 20.6 [17.7–23.6±33.6] days; *P*=0.7). Similar results were observed in patients who did not receive growth factors (no statistically significant differences).

Non-hematologic adverse effects and transplant-related mortality

The overall incidence of organ toxicity associated with HDT was 72% (162 patients) with BUMEL and 69% (373 patients) with MEL200 (*P*=0.4). As shown in Table 2, the most relevant adverse effects were stomatitis, gastroin-

testinal toxicity and hepatotoxicity. One patient died from sudden arrhythmia and another from heart failure; these were reported as MEL200-related toxicities. Fever was reported in 168 (75%) and 386 (71%) patients in the BUMEL and MEL200 groups, respectively (*P*=0.2), predominantly associated with neutropenia. The frequency of bacteremia or other microbiological events was also similar between the two conditioning groups (BUMEL 31%, MEL200 27%; *P*=0.2).

With regards to VOD, 19 patients (8%) who received BUMEL compared with only two patients (0.4%) who received MEL200 had this complication (*P*<0.00001), as previously reported.²¹ Mortality was directly related to VOD in seven (3%) patients in the BUMEL group and in one (0.2%) patient in the MEL200 group (*P*=0.003). In addition, 12 patients (5.3%) treated with BUMEL died within 100 days of SCT from causes other than MM (9 septic complications, 1 intracranial hemorrhage, 1 ischemic central nervous system stroke, 1 cause unknown), compared with 16 patients (2.9%) in the MEL200 group (13 sepsis, 1 CNS hemorrhage, 1 engraft-

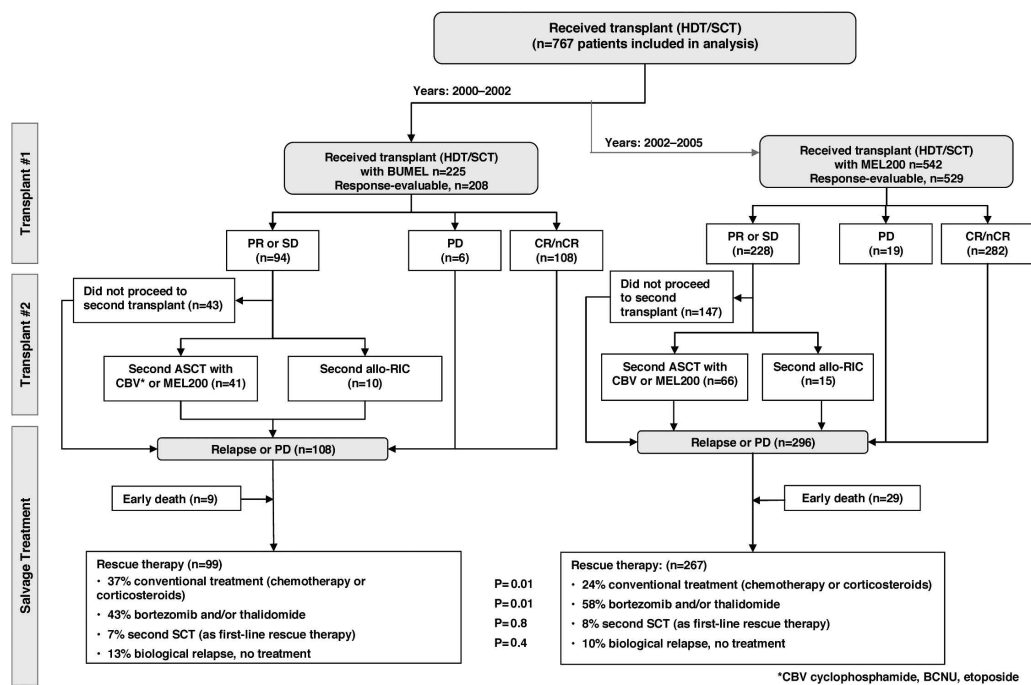


Figure 1. Patient flow through the GEM2000 study protocol for the 767 patients included in this analysis, including salvage treatment received in patients who relapsed/progressed.

Table 2. Non-hematologic toxicity (excluding VOD) due to high-dose regimens.

	Grade I		Grade II		Grade III		Grade IV*		II/III differences <i>P</i>
	BUMEL	MEL200	BUMEL	MEL200	BUMEL	MEL200	BUMEL	MEL200	
Cardiac	2 (0.8)	2 (0.3)	3 (1.3)	8 (1.4)	–	7 (1.2)	–	2 (0.3)	0.2
Renal	–	2 (0.3)	3 (1.3)	8 (1.4)	3 (1.3)	3 (0.5)	–	–	0.2
Pulmonary	–	1 (0.1)	1 (0.4)	2 (0.3)	1 (0.1)	3 (0.5)	–	–	0.6
Hepatic	10 (4.4)	9 (1.6)	6 (2.6)	1 (0.1)	1 (0.1)	–	–	–	0.0004
Central nervous system	–	1 (0.1)	2 (0.8)	5 (0.9)	–	1 (0.1)	–	–	0.7
Stomatitis	19 (8.4)	53 (9.7)	73 (32.4)	141 (26.0)	21 (9.3)	34 (6.7)	–	–	0.01
Gastrointestinal	5 (2.2)	45 (8.3)	10 (4.4)	34 (6.7)	2 (0.8)	11 (2.0)	–	–	0.09

*Fatal toxicity; VOD: veno-occlusive disease; BUMEL: oral busulfan 1 mg/kg/8 h plus melphalan 140 mg/m²; MEL200: 200 mg/m².

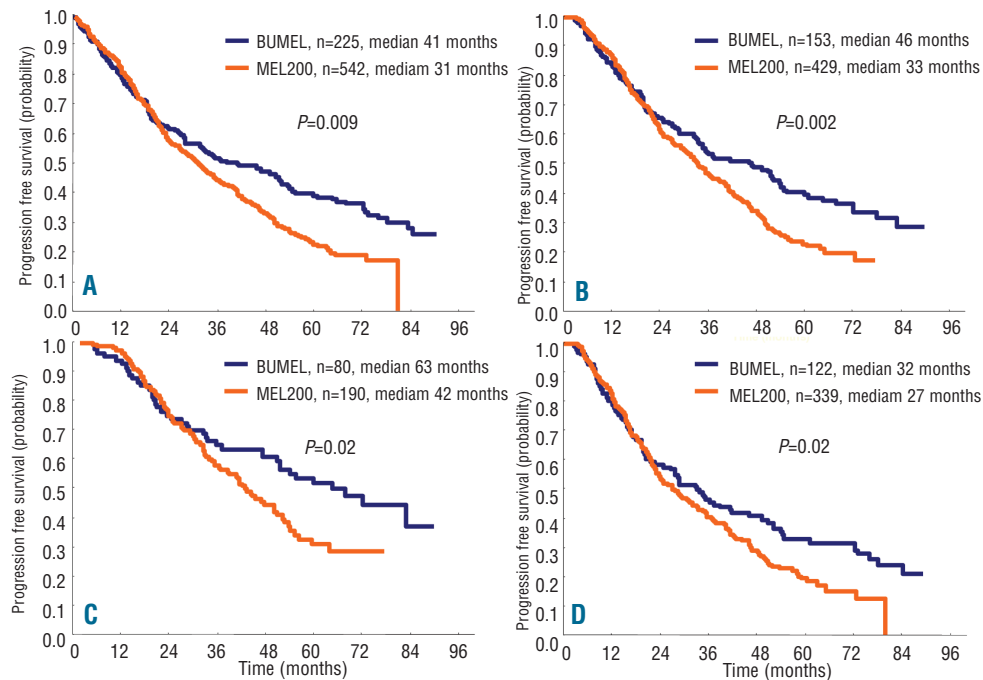


Figure 2. Progression-free survival according to conditioning regimen among (A) all patients; (B) all patients excluding those treated with autologous or allogeneic tandem transplantation; (C) only patients achieving complete response after HDT/SCT; (D) patients achieving less than complete response after HDT/SCT.

ment syndrome, 1 suicide). The overall transplant-related mortality rate was 8.4% (19 patients) and 3.5% (19 patients) in the BUMEL and MEL200 groups, respectively ($P=0.002$). Excluding VOD, this difference was not statistically significant ($P=0.1$).

Post-transplant responses

Post-transplant responses were equivalent in evaluable patients who received BUMEL (n=208) and MEL200 (n=529): 38% complete response, 13% near complete response, 39% partial response, 6% stable disease, 3% progressive disease, and 36% complete response, 17% near complete response; 39% partial response, 5% stable disease, 4% progressive disease, respectively ($P=0.9$ to 0.1). In addition, there were no statistically significant differences in the rates of improvement in response between the conditioning regimens when patients were stratified by pre-HDT/SCT status (*data not shown*).

Survival analyses

Progression-free survival

After a median follow-up of 72 and 47 months, respectively, the median progression-free survival was 41 months for patients who received BUMEL and 31 months for those who received MEL200. At 5 years, 39% (88 patients, 95% CI: 34–44%) of patients in the BUMEL group remained progression-free compared to 21% (114 patients, 95% CI: 18–24%) in the MEL200 group ($P=0.009$; Figure 2A). A similar pattern was observed when tandem transplant patients were excluded ($P=0.002$; Figure 2B) or when only patients with complete response ($P=0.02$; Figure 2C) or less than complete response ($P=0.02$; Figure 2D) as their post-transplant response were considered.

Overall survival

Patients treated with BUMEL or MEL200 had similar overall survival; the median overall survival was 79 and 71

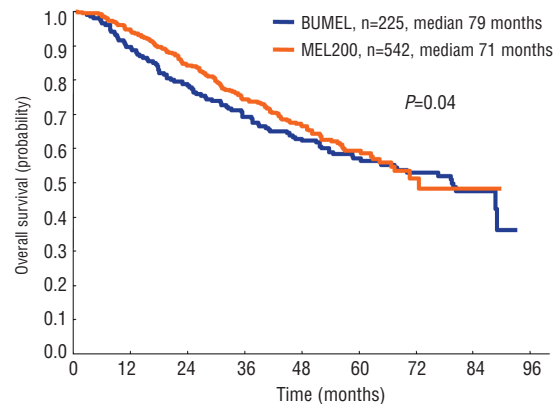


Figure 3. Overall survival according to conditioning regimen.

months, and 5-year rates were 55% (124 patients, 95% CI: 45–60%) and 57% (309 patients, 95% CI: 54–60%), respectively (Figure 3). No differences between the BUMEL and MEL200 groups in median overall survival were observed when patients who received a tandem transplant were excluded (77 versus 70 months, $P=0.4$), when the analysis focused on those patients achieving complete response after transplant (82 months versus not reached, $P=0.3$), or when only patients who did not achieve complete response were analyzed (64 versus 63 months, $P=0.5$).

Influence of salvage therapy on survival

At data cut-off, 99 (44%) and 267 (49%) patients in the BUMEL and MEL200 groups, respectively, had received salvage therapy (Figure 1). The different periods of recruitment for patients in the BUMEL (2000–2002) and MEL200 (2002–2005) groups resulted in disparate access to rescue therapies at relapse/progression. Among patients who received salvage therapy in the BUMEL and MEL200 groups, 37% and 24%, respectively, received conventional

treatments such as chemotherapy or corticosteroids ($P=0.01$). In contrast, 43% and 58% of patients in the BUMEL and MEL200 groups, respectively, received bortezomib and/or thalidomide-based combinations as salvage therapy ($P=0.01$). A second HDT/SCT was used as first-line rescue treatment in 7% and 8% ($P=0.8$) of patients in the BUMEL and MEL200 groups, respectively. At data cut-off, 13% and 10% of patients in the BUMEL and MEL200 groups, respectively ($P=0.4$), had biological relapses but had not yet received salvage treatment.

Regardless of conditioning regimen, among patients who had relapsed/progressed, overall survival was significantly longer in patients who received thalidomide and/or bortezomib-based salvage therapy (5-year overall survival rate: 38%) than in patients who did not (5-year overall survival rate: 13%; $P<0.0001$).

Finally, an adjusted multivariate analysis for overall survival was performed in relapsing patients (Cox model χ^2 31.8, $P=0.00004$) and it was found that both use of thalidomide or bortezomib as salvage therapy (OR 2.2, $P=0.000001$) and BUMEL (OR 1.4, $P=0.04$) as the conditioning regimen showed independent positive prognostic influence on disease outcome with respect to use of chemotherapy or corticosteroids at relapse/progression (OR 0.4) or MEL200 (OR 0.7) as the conditioning regimen.

Discussion

The use of HDT followed by stem cell support is a standard of care for young, newly diagnosed MM patients³³ and MEL200 has become the undisputed standard conditioning regimen. Research into improving HDT/SCT efficacy using agents such as cyclophosphamide, thiotepa, BCNU, dacarbazine, idarubicin or etoposide has so far proved inconclusive.^{16,34-37} Only BUMEL has been associated with some benefit compared with MEL200, although the studies had limited power to demonstrate a difference.^{19,20,38} Recently the IFM group reported on the efficacy of adding bortezomib to MEL200 as part of the conditioning regimen, resulting in a significant increase in complete response rate as compared to that with only MEL200 in a matched control historical comparison (35% *versus* 11% complete responses, respectively).¹⁷

Based on the findings of two retrospective GEM studies showing higher complete response rates and longer, albeit not statistically significantly, so, event-free survival and overall survival with BUMEL than with MEL200, BUMEL was selected as the initial conditioning regimen in GEM2000. However, after an interim analysis²¹ demonstrating a high incidence of late VOD (8%) with an unusually high mortality (8.4%), BUMEL was replaced by MEL200. After this protocol amendment the incidence of VOD fell to 0.4%. The erratic pharmacokinetics of oral busulfan³⁹ and the altered clearance of melphalan caused by the depletion of intracellular glutathione, induced by busulfan,⁴⁰⁻⁴² may have caused this complication. Some studies have shown that adjusting the oral busulfan dose according to plasma levels may lead to a reduction in the frequency of VOD.⁴³

An alternative to oral busulfan is intravenous busulfan, which results in more stable plasma levels.⁴⁴ Use of high dose intravenous busulfan in combination with cyclophosphamide and other drugs in the context of autologous or allogeneic transplantation for acute leukemia and

non-Hodgkin's lymphoma has drastically reduced the incidence of VOD while maintaining efficacy.³⁹ In a recent Spanish phase II pilot study⁴⁵ including both relapsed and newly diagnosed MM patients, none of the patients given intravenous BUMEL/SCT developed VOD and the complete/near complete response rate post-transplant was 49%. The possibility of maintaining efficacy with intravenous busulfan while reducing or eliminating VOD renewed our interest in the GEM2000 results, presented herein after a median follow-up of 48 months.

In GEM2000, when patients with VOD were excluded, there were no differences between BUMEL and MEL200 regarding engraftment and duration of hospitalization – the only significant differences were in the incidences of stomatitis and hepatotoxicity. It is doubtful that these differences are of clinical significance: the frequency of grade III stomatitis was 9.3% with BUMEL and 6.7% with MEL200, and only one of 225 patients treated with BUMEL had grade III hepatotoxicity other than VOD. In contrast, two patients receiving MEL200 died from cardiotoxicity.

In terms of efficacy, the most relevant finding in this analysis was the longer progression-free survival seen in the BUMEL group (median 41 months) compared with the MEL200 group (31 months), an improvement that persisted even when tandem transplantation patients were excluded. This effect was not detected in an earlier analysis⁴⁶ as the PFS curves overlapped for first 24 months and only separated after this point. Because response rates were similar with both regimens and the advantage of BUMEL over MEL200 was maintained in patients achieving complete response or less than complete response, it can be concluded that the difference in progression-free survival is, in part, either independent of the depth of the response or that the conventional methods used for complete response assessment were not sensitive enough to detect deep responses.²⁵ Alternatively, combining alkylating agents might target dormant tumor cells, including tumor stem cells, more specifically, thus impeding or delaying tumor progression resulting from this 'pharmacologic sanctuary'.⁴⁷

The advantage in progression-free survival seen with BUMEL did not extend to overall survival. One possible explanation is that overall survival in MM is dependent on the effects of subsequent lines of therapy as salvage treatment and thus the value of overall survival as an end-point in MM is questionable. Of note, in the GEM2000 study, BUMEL conditioning was given between 2000 and 2002 with patients being switched to MEL200 after 2002. These differences in dates explain why the access to novel agents as treatments for relapse/progression was less frequent in patients previously treated with BUMEL than in those treated with MEL200. This disparity in our study, as observed in other studies,⁴⁸ may have had a significant impact on overall survival. Although in our study patients receiving thalidomide or bortezomib at the time of relapse had a significantly longer overall survival than that of patients rescued with conventional chemotherapy this comparison should be qualified with the caveat that patients had to live longer to get to the novel agent therapies and that by itself would put those patients who managed to do so in a better position in terms of disease biology. Nevertheless, in the multivariate analysis it was found that both the conditioning regimen (BUMEL *versus* MEL200) and the type of rescue therapy (novel agents *ver-*

sus conventional chemotherapy) were independent prognostic factors for overall survival in relapsing patients.

While the study has limitations due to its sequential nature, other study characteristics such as its prospective nature, large sample size, length of follow-up, and homogeneity of inclusion criteria, and induction and post-transplantation treatments, clearly contribute positively to the value of this work. Thus, in conclusion, despite the effects of possible confounding factors, the results of our analysis suggest that BUMEL may have greater anti-myeloma activity than MEL200; however, this should be balanced against its higher toxicity profile and transplant-related mortality, at least with the oral formulation of busulfan. Taken together, our data support a future phase III study comparing intravenous BUMEL to MEL200 in the context of autologous transplantation as first-line treatment for young MM patients.

Authorship and Disclosures

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Appendix

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