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Phase II Trial of Allogeneic Transplantation Plus Novel Drugs in Multiple Myeloma: Effect of Intensifying Reduced-Intensity Conditioning with Bortezomib and Adding Maintenance Treatment

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A B S T R A C T

The use of reduced-intensity conditioning (RIC) regimens has decreased the risk of nonrelapse mortality (NRM) after allogeneic stem cell transplantation (alloSCT). In contrast, disease relapse remains the most frequent cause of treatment failure and death. Owing to both their antimyeloma effect and immunomodulatory properties, novel drugs could improve outcomes after alloSCT. This phase II European Myeloma Network trial was designed to evaluate the combination of alloSCT with novel agents. The study was conducted to evaluate the toxicity and efficacy of RIC intensified with bortezomib (Bz) prior to alloSCT for high-risk (HR) multiple myeloma (MM) patients, as well as the efficacy of post-transplantation maintenance with Bz and lenalidomide (Len). Patients received RIC with Bz on days -9 and -2, fludarabine on days -6 to -4, and melphalan on day -3. Patients who were in complete response (CR) or near CR at day +100 post-transplantation received 6 cycles of Bz every 56 days, and the remaining received Bz, Len, and dexamethasone. Len maintenance was started on day +180 at a dose of 5 mg and continued until relapse or toxicity occurred. Of the 24 patients included, 21 were evaluable on day +100, including 12 in CR, 4 in very good partial response, 3 in partial response, and 2 with relapse or progression. The cumulative incidence (CuI) of relapse was 13.6% (95% confidence interval [CI], 3.2% to 31.3%) at 1 year and 28.5% (95% CI, 11.1% to 48.9%) at 2 years. The CuI of NRM was 21.1% (95% CI, 7.4% to 39.4%) at 2 years. With a median follow-up of 39 months (range, 1 to 67 months), the median event-free survival (EFS) was 29 months, and median overall survival (OS) was not reached. EFS and OS at 3 years were 42.5% (95% CI, 21.9% to 61.7%) and 74.01% (95% CI, 50.9% to 87.5%), respectively. The use of Bz within an RIC regimen allows for a high response rate after alloSCT. Maintenance with Bz and Len is feasible and provides remarkable results in terms of EFS and OS in HR MM patients.

INTRODUCTION

Despite advancement in the treatment of multiple myeloma (MM) over the past 20 years [1–3], most patients ultimately relapse and die from resistant disease. Allogeneic stem cell transplantation (alloSCT) has provided a cure for some patients through an immune-mediated graft-versus-myeloma (GVM) effect [4–6]; however, its use is controversial owing to the high risk of mortality and toxicity related to therapy

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[2,7,8]. Different consensus guidelines have been proposed indicating that alloSCT could be an appropriate therapy for MM patients with early relapse (<24 months) after primary therapy (including autologous stem cell transplantation [autoSCT]) and/or with high-risk (HR) features and should be performed in the setting of clinical trials. Prospective trials evaluating post-alloSCT maintenance treatment and its role as salvage therapy are needed [9].

Although the use of reduced-intensity conditioning (RIC) has greatly reduced nonrelapse mortality (NRM) [10,11], neither the incidence of graft-versus-host disease (GVHD) nor the relapse rate (RR) have been reduced. In fact, the RR seems to be even higher with the use of RIC [12,13]. To reduce the incidence of relapse after alloSCT, some therapeutic strategies have been explored, including consolidation or maintenance therapy, most commonly at relapse [14]. Bortezomib (Bz), the first proteasome inhibitor (PI) approved for the treatment of MM [15], has a direct antitumor effect and also exerts strong effects on nonneoplastic immune cells. In preclinical models, we and others have described its proapoptotic effect on activated T cells while preserving the viability of resting and regulatory T cells [16,17].

We recently published a phase I trial designed to evaluate the safety and efficacy of i.v. Bz as part of the conditioning regimen, as well as in combination with sirolimus and tacrolimus for GVHD prophylaxis in MM patients with a poor prognosis. Remarkably, at 3 months after transplantation, out of 21 evaluable patients, 67% were in complete response (CR), and 33% were in partial response (PR). NRM was 24% at 1 year (95% confidence interval CI, 9.4% to 42.2%). RR at 1 year was 21.4% (95% CI, 4.7% to 45.9%). Overall survival (OS) and event free survival (EFS) at 2 years were 64% and 31%, respectively [18].

Several studies have reported a RR in the range of 42-55% [12,13]. The response rate previously reported is rather high (up to 40% CR plus 35-45% PR). In an attempt to decrease the risk of relapse, we designed a phase II trial maintaining the same Bz-intensified RIC and a GVHD prophylaxis based on the combination of tacrolimus, methotrexate (MTX), and Bz but adding maintenance with Bz and Lenalidomide (Len) in HR MM patients candidates for alloSCT. Our goal was to maintain the overall response rate (ORR) (increasing the CR rate) and decrease the RR.

METHODS

Study Design

The conditioning regimen comprised Bz 1.3 mg/m^2 i.v. on days -9 and -2, fludarabine 30 mg/m^2 i.v. on days -6 to -4, and melphalan 140 mg/m^2 i.v. on day -3. The infusion of hematopoietic progenitor stem cells (at a recommended dose of $>5 \times 10^6$ CD34$^+$ cells/kg) was performed on day 0. GVHD prophylaxis was based on Bz 1.3 mg/m^2 i.v. on days +1, +4 and +7; MTX 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6 and +11; and tacrolimus 0.03 mg/kg/day i.v. started on day -3 to maintain levels in the range of 5 to 10 ng/mL, switching to oral administration as tolerated. A slow taper was started on day +50 (±10 days). Two recipients of alloSCT with a matched unrelated donor received antithymocyte globulin. To address drug-related toxicity, safety rules were proposed to decrease the dose of Bz to 1 mg/m^2 on days +1, +4, and +7 in the event of grade 3-4 peripheral neuropathy >20% or grade 3-4 gastrointestinal toxicity >20%. For maintenance, patients received Bz 1.3 mg/m^2 i.v. on days +1, +8, and +15 in 28-day cycles starting on day +70 post-transplantation. Patients in CR at day +100 received Bz 1.3 mg/m^2 on days +1, +8, and +15 in cycles of 56 days up to 6 cycles, with Len 5 mg started on day +180 and continued until relapse or toxicity occurred. The remaining patients received 4 cycles of VRD (Bz 1.3 mg/m^2 days +1, +8, +15; Len 15 mg day on days +1 to +21; plus dexamethasone 10 mg on days +1 to +4 and days +8 to +11) every 28 days. On day +180, these patients continued with the same maintenance therapy as described for patients in CR. The original trial was registered at ClinicalTrials.gov (identifier NCT01460420) and at EudraCT (2010-018594-37). The protocol was approved by local Ethics Committees of the participating centers. All procedures were conducted in accordance with the Declaration of Helsinki.

Patient Eligibility

Adult patients age 18 to 70 years with HR MM at first relapse (FR)/second CR who were candidates for alloSCT were eligible for this study. Subsequent relapses were allowed owing to low patient accrual. Patients must have had a suitable related or unrelated donor and measurable disease. HR FR was defined as early FR after autoSCT (<24 months) or FR in patients with poor cytogenetic features, as well as late FR in patients who did not achieve CR after a second autoSCT. All patients provided written informed consent before trial entry.

Exclusion criteria are described in Supplementary Data, Methods S1.

Safety and Efficacy Analysis

Safety was evaluated by assessing adverse events in all patients from the first procedure related to the study until 30 days after the end of the treatment period, at least 1 year after transplantation. The severity of adverse events was assessed according to the National Cancer Institute's Common Toxicity Criteria, version 4.0.

Further information concerning safety and efficacy analysis, biological procedures, and statistical analysis is available in Supplementary Data, Methods S2 to S4.

RESULTS

Patient Characteristics

Twenty-four patients were included into the trial between 2012 and 2017. Their median age was 48.5 years (range, 27 to 69 years). The most common MM subtype was IgG, followed by IgA and light-chain multiple myeloma. The median number of previous treatment lines was 2 (range, 1 to 5); all patients had previously received treatment with PI and immunomodulatory drugs (IMiDs). Three patients were previously refractory to Bz, and 1 patient was refractory to Len. Twenty-one patients (87% of the total) had undergone previous autoSCT. Six patients had extramedullary disease at the time of inclusion into the trial. With regard to cytogenetic alterations, data were available for 19 patients, of whom 17% had HR features: del17p, t(4;14), or t(14;16). Patient characteristics are summarized in Table 1.

At the time of transplantation, 9 patients were in CR, 7 were in very good partial response (VGPR), 7 were in PR, 1 had stable disease, and none had progressive disease. AlloSCT was performed using a matched related donor in 11 patients, a matched unrelated donor in 11 patients, and a mismatched unrelated donor in 2 patients. The median infused CD34$^+$ cell dose was 5.75 $\times$ 10^6/kg (range, 4 to 9.9 $\times$ 10^6/kg) (Table 2).

Table 1
Patient Characteristics

Characteristic	Value
Age, yr, median (range)	48 (27-69)
Type of MM, n (%)	
IgG	10 (42)
IgA	8 (33)
Light chain only	6 (25)
Previous lines of treatment	
Number (median, range)	2 (1-5)
1, n (%)	2 (8)
2, n (%)	11 (46)
≥3, n (%)	11 (46)
Previous PI, n (%)	24 (100)
Previous immunomodulatory drug, n (%)	24 (100)
Previous autograft, yes/no, (%)	21/3 (87/13)
Extramedullary disease, yes/no, n (%)	6/18 (25/75)
Cytogenetics, n (%)	
High risk: del17p, t(4;14), or t(14;16)	4 (17)
Standard risk	15 (62)
NA	5 (25)

PI, proteasome inhibitor, NA indicates not available.

Table 2
Disease Status at Transplantation and AlloSCT Characteristics

Parameter	Value
Disease status at transplantation, n (%)	
CR	9 (38)
VGPR	7 (29)
PR	7 (29)
SD	1 (4)
Type of donor, n (%)	
MRD	11 (44)
MURD	11 (44)
MMURD	2 (12)
Infused CD34$^+$ cell dose, $\times 10^6$/kg, median (range)	5.75 (4-9.9)
Engraftment	
Neutrophils, yes/no, n	22/0
Days to engraftment $\geq 500 \times mm^3$, median (range)	14 (10-23)
Platelets, yes/no, n	20/2
Days to engraftment $\geq 20{,}000 \times mm^3$, median (range)	14 (7-59)
Early toxicity ($\leq$100 days post-transplantation), n (%)	
Mucositis grade 3-4	3 (13)
Gastrointestinal grade 3-4	5 (16)
TMA	1 (4)
CNS grade 3-4	2 (8)
Infections	8 (33)
aGVHD grade 11-1V/III-IV, n (%)	12 (50)/6 (25)
cGVHD (NIH grade), mild/moderate/severe, n (%)	1 (4)/5 (21)/1 (4)

SD indicates stable disease; MRD, matched related donor; MURD, matched unrelated donor; MMURD, mismatched unrelated donor; TMA, thrombotic microangiopathy; CNS, central nervous system;

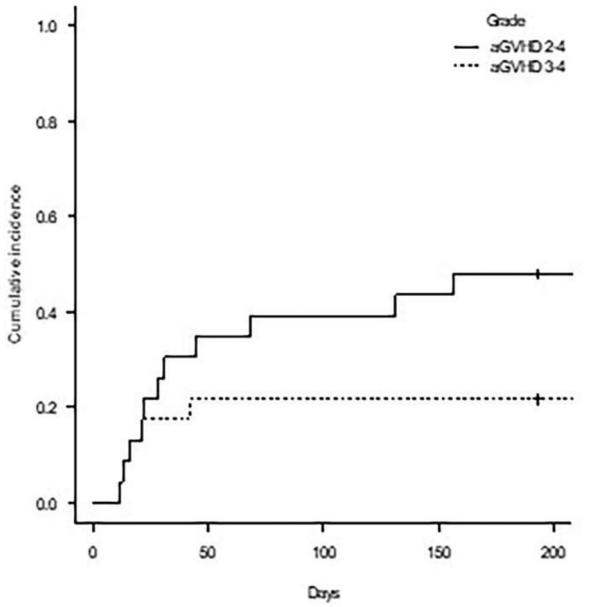

Figure 1. CuI of aGVHD. The dashed line represents aGVHD grade III-IV; the solid line, grade II-IV.

Engraftment, Toxicity, and GVHD

Information about engraftment was available for 22 patients, all of whom reached a neutrophil count of $>0.5 \times 10^6$/L at a median of 14 days (range, 10 to 23 days). Twenty patients achieved a platelet count of $>20 \times 10^6$/L, at a median of 14 days (range, 7 to 59 days).

Early toxicity was recorded from the day of alloSCT until 100 days post-transplantation. Nineteen adverse events were reported. Three patients developed grade 3-4 mucositis necessitating the use of total parenteral nutrition. One patient developed paralytic ileus, and 1 patient had melaena and hematemesis associated with postinfusion aplasia. Three other patients had diarrhea. As for infections, the most frequently recorded events were febrile neutropenia with no focus (n = 4; 16%) in the first days after transplantation, one patient each developed sepsis, central venous catheter infection, pneumonia, and cytomegalovirus infection. In terms of central nervous system toxicity, 1 patient suffered unknown origin encephalopathy that subsequently resolved, and 1 patient had an episode of diplopia in the context of noninfectious febrile syndrome and grade 2 headache. One patient developed thrombotic microangiopathy that was treated with plasma replacement and eculizumab. No early skin adverse events were reported (Table 2).

Twelve patients developed grade II-IV acute GVHD (aGVHD), including 6 patients with grade II, 2 with grade III, and 4 with grade IV). The cumulative incidence (CuI) of aGVHD at 100 days was 39% (95% CI, 15.5% to 56.1%) for those with grade II-IV aGVHD and 21.7% (95% CI, 7.7% to 40.4%) for those with grade III-IV aGVHD (Figure 1). Chronic GVHD (cGVHD) was mild in 1 patient (4%), moderate in 5 patients (21%), and severe in 1 patient (4%). The CuI of overall cGVHD at 1 year was 22.7% (95% CI, 7.9% to 42%), that of moderate-severe cGVHD was18.1% (95% CI, 5.4% to 36.8%), and that of severe cGVHD was 4.6% (95% CI, 0.3% to 19.6%) (Figure 2).

Response and Relapse Rates and Overall Outcomes

The response rate at day +100 was evaluated in 21 patients; 3 patients died before the day +100 evaluation due to aGVHD.

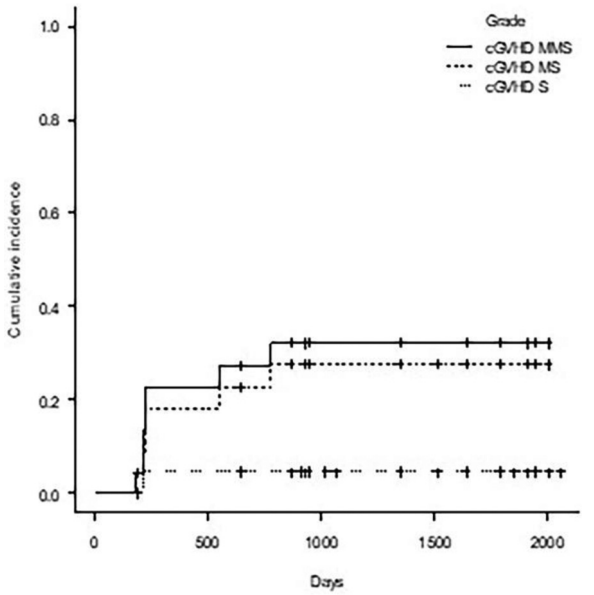

Figure 2. CuI of cGVHD. MMS, mild-moderate-severe; MS, moderate-severe; S, severe.

Table 3
Patient Outcomes

Patient	Disease Status at Transplantation	Response at Day +100	Relapse, months	aGVHD	cGVHD	NRM	Status at Last Follow-Up
1 (0105)	PR	N/E	No	Grade IV	No	Yes	Dead
2 (0106)	VGPR	sCR	No	No	No	No	CR, alive
3 (0107)	VGPR	sCR	No	No	Mode	No	CR, alive
4 (0119)	VGPR	VGPR	Yes (19)	Grade I	Mode	No	CR, alive
5 (0120)	CR	CR	No	Grade IV	No	Yes	Dead
6 (0121)	CR	sCR	No	No	No	No	CR, alive
7 (0212)	CR	N/E	No	Grade III	No	Yes	Dead
8 (0501)	VGPR	PR	Yes (22)	No	Mode.	No	Dead
9 (0503)	CR	CR	No	No	No	No	CR, alive
10 (0505)	SD	N/E	No	Grade IV	No	Yes	Dead
11 (0506)	PR	CR	No	Grade I	No	No	CR, alive
12 (0701)	PR	PR	No	Grade IV	No	Yes	Dead
13 (0702)	VGPR	VGPR	No	No	No	No	CR, alive
14 (1001)	PR	PR	Yes (11)	Grade II	No	No	Relapse, alive
15 (1002)	CR	CR	Yes (18.5)	Grade II	No	No	Relapse, alive
16 (1102)	PR	sCR	No	No	Seve	No	CR, alive
17 (1103)	VGPR	PD	Yes (3)	Grade II	No	No	Dead
18 (1104)	CR	CR	No	No	No	No	CR, alive
19 (1105)	CR	CR	No	Grade II	Mode	No	CR, alive
20 (1201)	PR	PD	Yes (2)	Grade II	No	No	VGPR, alive
21 (1202)	PR	VGPR	No	No	Mild	No	CR, alive
22 (1601)	CR	CR	Yes (29)	No	No	No	Relapse, alive
23 (1602)	CR	sCR	No	Grade II	Mode	No	CR, alive
24 (1604)	VGPR	VGPR	Yes (34)	Grade III	No	No	Relapse, alive

PD indicates progressive disease; TRM, treatment-related mortality; mode moderate; seve severe.

At day +100, 12 patients (50%) were in CR, 4 (17%) were in VGPR, 3 (12.5%) were in PR, and 2 (8%) had relapsed or progressed (percentages refer to the total study population). Of the 8 evaluable patients in CR at the time of transplantation, 6 maintained this status and 2 showed an improved response, achieving stringent CR (sCR). Of the 7 patients with VGPR, 1 patient progressed, 2 patients improved their response by achieving sCR, 3 patients maintained VGPR, and 1 patient was in PR. Of the 6 evaluable patients who were in PR at the time of transplantation, 3 patients improved their response (1 in sCR, 1 in CR, and 1 in VGPR), 2 patients maintained a PR on day +100, and 1 patient progressed within 2 months post-transplantation (Table 3). Interestingly, none of the patients with HR cytogenetics relapsed, and all were in CR at last follow-up (1 patient died on day +145 from grade 4 aGVHD).

At a median follow-up of 39 months (range, 1 to 67 months), 7 patients had died (5 due to aGVHD and 2 due to MM progression) and 8 had relapsed, with a median time to relapse of 19 months (range, 2 to 34 months). The CuI of NRM was 21.1% (95% CI, 7.4% to 39.4%) at 2 years (Figure 3A). The CuI of relapse was 13.6% (95% CI, 3.2% to 31.3%) at 1 year and 28.5% (95% CI, 11.1% to 48.9%) at 2 years (Figure 3B). The median EFS was 29 months (95% CI, 8.1% to 49.8%); it was not reached for patients who achieved CR or VGPR. The 2-years EFS was 52.6% (95% CI, 30.8% to 70.4%), and 4-year EFS was 42.5% (95% CI, 21.9% to 61.7%) (Figure 4). The median OS has not been reached at the time of this report, and 2-year and 4-year OS were 78.9% (95% CI, 56.6% to 90.7%) and 74.01% (95% CI, 50.9% to 87.5%), respectively (Figure 5).

Among the 20 patients evaluable for maintenance therapy (excluding the 4 patients who died before day +180), 14 (70% of this cohort) did not proceed to maintenance therapy or stopped it before relapse or death due to patient choice (n = 1), aGVHD (n = 5), cGVHD (n = 4), cytopenia (n = 1), infection (n = 1), or neuropathy (n = 2) (Supplementary Table S1). Two of the 5 patients who developed aGVHD did so before receiving maintenance therapy, and the other 3 did so after receiving Bz. In the 4 patients who developed cGVHD, consolidation therapy was provided with VRD in 1 patient, with Bz in 1 patient, and with Bz and Len in 2 patients. One patient received a donor lymphocyte infusion at relapse on day +77 post-transplantation. Characteristics of post-transplantation treatments are summarized in Supplementary Table S2.

Immune Recovery and Minimal Residual Disease Monitoring

We analyzed the immune cell populations in peripheral blood samples of 9 patients. No relevant differences in absolute counts (per μL) were observed at days +100, +180, +270 and +365 post-transplantation (Supplementary Figure S1A-D, Supplementary Table S3).

To investigate whether maintenance treatment could influence immune recovery, we compared these results with those of a cohort of 12 patients included in the European Myeloma Network (EMN) phase I trial who did not receive Bz or Len after transplantation. The median count of monocytic dendritic cells was slightly inferior in patients who received maintenance therapy on days +100 (0.03 versus 0.07; $P = .042$), +180 (0.02 versus 0.05; $P = .041$), and +270 (0.024 versus 0.233; $P = .029$). However, global lymphocyte count was superior on days +100 (2.25 versus 1.16; $P = .022$) and +270 (2.31 versus 1.29; $P = .045$). Within the different lymphocyte subpopulations, patients in phase I had superior levels of naïve T CD4 cells (0.219 versus 0.044; $P = .04$) and CD8 cells (0.132 versus 0.025; $P = .004$) at day +365 but lower levels of peripheral

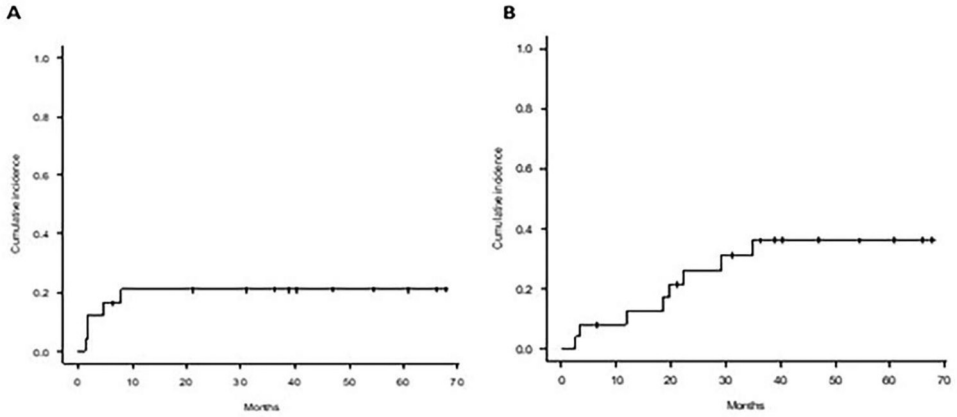

Figure 3. CuI of NRM (A) and relapse (B) calculated with the cmprsk package for R version 2.14.0. The competing event for NRM was relapse.

memory T CD8 cells at day +270 (0.092 versus 0.546; $P = .033$). Regulatory T cell levels were superior in patients included in the phase II trial on days +100 (0.031 versus 0.007; $P = .002$) and + 270 (0.05 versus 0.01; $P = .002$). No statistically significant differences were seen in other lymphocyte subpopulations, natural killer (NK) cells, and dendritic cells (Supplementary Figure S2, Supplementary Table S4). This analysis was limited, however, given the differences in GVHD prophylaxis between the 2 trials. We also compared the different immune cell subpopulations in the patients included in the phase II trial based on the development or nondevelopment of GVHD and found no significant differences, likely owing to the low number of samples available (Supplementary Table S5).

Minimal residual disease (MRD) was monitored by local laboratories using flow cytometry. Follow-up data were available for 14 patients starting on day +28. Eight of these patients were positive for MRD (range, 0.52% to 0.0017% of total bone marrow cells); on day +100, 2 patients became MRD-negative and 5 remained MRD-positive, 4 of whom relapsed during follow-up and 1 of whom died due to aGVHD. Of the 6 MRD-negative patients on day +28, 2 died before day +100, 2 remained MRD-negative until their last follow-up, and the other 2 remained negative up to 1 year post-transplantation, although both subsequently relapsed, at 29 and 34 months.

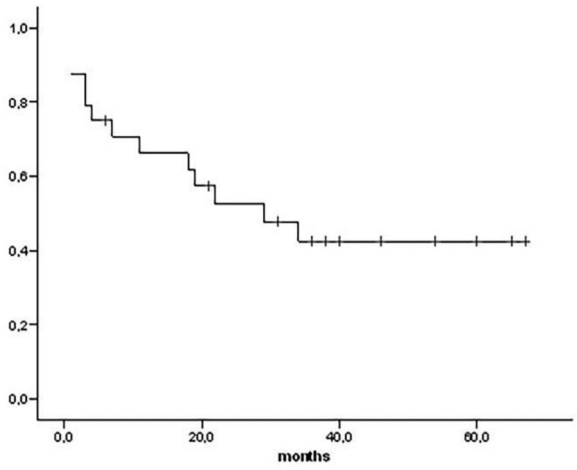

Figure 4. EFS, calculated from the time of transplantation to relapse or death. Nonachievement of at least partial response at any time after transplantation also was considered an event.

DISCUSSION

Over the last 2 decades, novel drugs have been incorporated into the treatment of MM, which has led to improved OS [3] and more durable responses, reaching a median progression free survival (PFS) of up to 45 months with some combinations of novel agents in patients who previously received at least 1 line of treatment [19]. In addition, a variety of immune-based therapies, including chimeric antigen receptor T cells, bispecific antibodies, antibody drug conjugates, and checkpoint inhibitors, have emerged as promising approaches in the setting of relapsed and/or refractory MM [20,21]. The use of high-dose chemotherapy followed by autoSCT is the standard of care for transplantation candidates with newly diagnosed MM [22]. In contrast, the use of alloSCT is controversial owing to the high risk of NRM, ranging from 17% to 25% [23], and alloSCT is currently recommended as salvage therapy in selected HR patients in the setting of clinical trials [9,24,25].

Through ubiquitin-proteasome pathway inhibition, Bz exerts a direct antitumor effect [16] by up-regulating proapoptotic proteins (eg, IkB1, Noxa) and suppressing prosurvival proteins (eg, Bcl-2, NF-κB) [26,27]. Proteasome inhibition also has immunomodulatory effects through inhibition of dendritic cells, as well as T and B cell subpopulations. Moreover, it suppresses the function of activated human $CD4^+$ T cells [16] while preserving the viability of resting and regulatory T cells [17]. Ixazomib, an oral second-generation PI, has demonstrated efficacy as GVHD therapy in a phase II trial including 50 patients

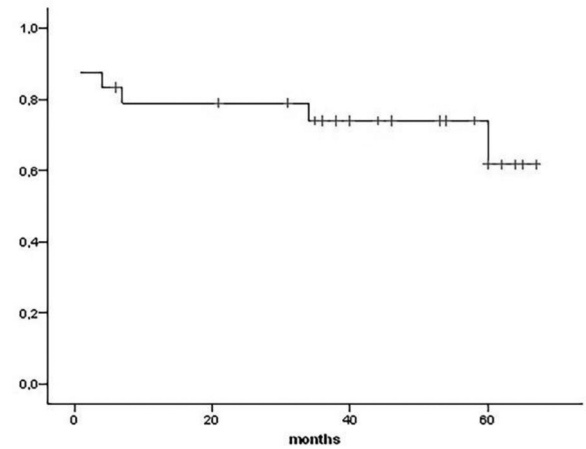

Figure 5. OS, calculated from the time of transplantation until death from any cause. Patients who survived were censored at their last follow-up.

with advanced cGVHD, with an ORR of 40% and a treatment failure rate of 28% at 6 months [28]. IMiDs such as Len and pomalidomide have demonstrated efficacy in the treatment of MM [19,29-31]. In addition to immune modulation properties, IMiDs also have antiangiogenic, anti-inflammatory and antiproliferative effects. They induce T cell proliferation and IL-2 and IFNγ production and enhance the cytotoxicity of NK and NKT cells [32]. Pomalidomide has been evaluated in a cohort of 34 patients with corticosteroid-refractory cGVHD, with an ORR of 67% at 6 months reported [33].

Owing to their antimyeloma effect and immunomodulatory properties, novel drugs could improve outcomes after alloSCT. In this regard, disease relapse remains the most frequent cause of death after alloSCT [14], and thus new strategies are needed to increase the effectiveness of the procedure. The EMN-I trial [18] was designed to evaluate the combination of alloSCT with novel agents. The conditioning regimen was intensified with Bz, and BZ also was used as GVHD prophylaxis with sirolimus and tacrolimus. Twenty-five patients were included. With a median follow-up of 33 months, 2-year OS and EFS were 64% (95% CI, 42% to 79%) and 31% (95% CI, 14% to 59%), respectively. The CuI of NRM was 24% at 1 year post-transplantation (95% CI, 9.4% to 42.2%) and the RR at 1 year was 21.4% (95% CI, 4.7% to 45.9%). Owing to this high RR, this phase II trial was planned with the objective of decreasing the risk of relapse by adding maintenance therapy with Bz and Len. This combination was associated with improved outcome post-alloSCT, with an RR at 1 year of 13.6% (95% CI, 3.2% to 31.3%) and OS and EFS at 2 years of 78.9% (95% CI, 56.5% to 90.6%) and 52.7% (95% CI 30.7% to 70.4%), respectively. Of course, this difference in RR also can be attributed to other variables, including patient characteristics, although both studies included only HR patients. For example, 20% of the patients in the phase I study were in CR at the time of transplantation versus 38% in the phase II study, and 80% in the phase I study had received $\geq$3 lines of therapy, compared with 46% in the phase II study.

Maintenance therapy has been shown to be effective after autoSCT. In a meta-analysis of 3 randomized control trials (RCTs) comparing Len maintenance post-transplantation versus placebo or observation, the first strategy showed a benefit in both PFS (52.8 months versus 23.5 months; hazard ratio [HR], 0.48; 95% CI, 0.41 to 0.55) and OS (median not reached versus 86 months; HR, 0.75; 95% CI, 0.63 to 0.90; P = .001) [34]. In addition, maintenance with Bz was evaluated in a meta-analysis of 2 RCTs in newly diagnosed MM patients, revealing an advantage in PFS (HR, 0.67; 95% CI, 0.51 to 0.87; P = .003) and OS (HR, 0.75; 95% CI, 0.63 to 0.89; P = .001) [35].

There are few published prospective trials evaluating maintenance therapy post-alloSCT. The Spanish Myeloma Group and the Spanish Hematopoietic Stem Cell Transplantation Group (GEM/GETH) conducted a clinical trial evaluating the safety and efficacy of Bz after alloSCT in a series of 16 patients with HR MM. Maintenance therapy with i.v. Bz was given to all patients starting at day +50 or +78 post-transplantation and continued for 7 cycles. The CuIs of NRM, relapse, and OS were 25%, 54% and 41%, respectively, at 3 years [36]. Green et al [37] used Bz (1.6 mg/m^2 i.v. or 2.6 mg/m^2 s.c. every 14 days for 9 months) after tandem auto/alloSCT in a prospective phase II trial including 31 HR MM patients either newly diagnosed or with relapsed or persistent disease. Of the 31 patients enrolled, 26 proceeded to alloSCT and 21 started maintenance therapy. Only 43% of the patients completed 9 months of Bz, with disease progression the reason for discontinuation in the majority. Newly diagnosed patients with HR features had CuIs of NRM, RR, PFS, and OS at 2 years of 8%, 21%, 71%, and 75%, respectively. Those who failed prior therapy had worse outcomes, with 2-year NRM, RR, PFS and OS of 14%, 71%, 14% and 43%, respectively. Recently, another phase II trial including 39 patients with poor prognostic MM used Bz as induction therapy before autoSCT and as maintenance (1.3 mg/m^2 every 2 weeks for 1 year) after tandem auto/alloSCT. Almost two-thirds (65%) of the patients had HR cytogenetics. At 3 years, NRM, PFS, and OS were 6%, 46%, and 92%, respectively. After alloSCT, Bz was shown to improve CR from 64% to 77% and to improve immunophenotypic CR (defined as sCR plus 2 consecutive negative MRD assessments) from 28% to 61% [38].

Other studies have evaluated maintenance with Len. In the HOVON-76 trial, 30 patients received post-alloSCT Len as part of first-line therapy starting at 3 months post-transplantation. The schedule of treatment was 10 mg of Len for 21 days in a 28-day cycle starting between 1 and 6 months post-transplantation. At 2 years, PFS was 60% and OS was 93%. Sixteen patients (53%) developed GVHD, including 11 with grade $\geq$II aGVHD and 5 with extensive cGVHD. Most patients stopped treatment prematurely (only 3 completed 24 cycles), and the authors concluded that maintenance therapy with 10 mg daily was infeasible, mainly because of the rapid induction of aGVHD [39].

In another phase I/II trial, Len was used as maintenance therapy for 1 year post-alloSCT in HR MM patients. The median time from transplantation to initiation of Len therapy was 96 days, with a planned dose of 10 mg/day for 21 days of a 28-day cycle and monthly dose escalation in 5-mg increments to a maximum of 25 mg/day. Twenty-nine patients were evaluable; 34% completed treatment, and 37% discontinued it owing to aGVHD. Four of the 14 patients who were not in CR at the start of maintenance therapy achieved CR after 2 to 5 cycles. The 1-year PFS and OS after initiation of Len therapy were 68% and 88%, respectively, with a CuI of 28% for progression and 3% for NRM [40].

A German group conducted a phase I/II trial of 24 MM patients receiving Len post-alloSCT at a median of 135 days post-transplantation for 4 cycles [41]. In 9 patients, GVHD was the main toxicity, with an overall incidence of 38%, and was the reason for stopping treatment in 29% of the patients. After a median follow-up of 15 months (range, 4 to 26 months), PFS and OS were 61% and 79%, respectively, at 2 years. The rate of CR improved from 24% to 42% after maintenance therapy. The authors also investigated immunologic parameters. Len did not influence the number of peripheral NK cells, but it enhanced their activation and improved their lytic activity against myeloma cells. In addition, a significant early increase in peripheral IFN-γ-secreting CD4$^+$ and CD8$^+$ T cells, followed by a delayed increase in regulatory T cells, was noted. Nonresponding patients showed less NK and T cell activation [41].

Kröger et al [42]. evaluated Len maintenance post-alloSCT in 24 patients who had relapsed after previous autoSCT. Thirteen patients had discontinued treatment, 6 because of progressive disease. The 1-year NRM was 6% (95% CI, 0 to 14%). The CuI of RR was 42% (95% CI, 18% to 66%) at 3 years, with a PFS of 52% and OS of 79%.

In another phase IIa trial, Len maintenance was started in a cohort of 30 patients with HR MM after alloSCT [43]. The primary endpoint was to determine the tolerability and safety profile. Eleven patients completed treatment, and 8 patients discontinued it early during or after the first cycle, with aGVHD and disease progression the most common reasons for discontinuation. The 3-year RR was 27% (95% CI, 13% to 44%). In this EMN-II prospective trial, patients received maintenance with

both Bz and Len. The 2-year CuI of RR of 28.5% (95% CI, 11.1% to 48.9%) was lower than that reported in the EMN-I trial, in which maintenance therapy was not provided. These values are in accordance with those in other studies in which Len was used post-alloSCT [40,42] but lower than those in studies that used Bz alone, in which RR ranged between 54% to 71% [36,37]. Seven patients completed maintenance treatment at least 1 year after transplantation; 5 of them were in CR at day +100, 3 received cycles of Bz and Len as planned by protocol without relapse at last follow up, 1 discontinued Len due to GVHD, and 1 stopped Bz due to neuropathy, with late relapse. Of the other 2 patients, who were in VGPR at day +100, 1 did not complete cycles of VRD due to GVHD, with relapse after 19 months post-alloSCT, and the other improved their response by achieving CR. In summary, out of 20 patients evaluable for maintenance therapy, 70% did not proceed to maintenance or stopped it before relapse or dead. The most common reason for discontinuation was GVHD, as was reported in the HOVON-76 trial [39] and other studies [40,41,43].

Regarding immune recovery post-transplantation, our cohort had several significant differences compared with the cohort of patients in the EMN-I trial who did not receive maintenance therapy, including the monocytic dendritic cell counts, overall lymphocyte counts, naïve CD4 and CD8 cell counts, and regulatory T cell counts. Although the present study was limited owing to the low number of available samples, and thus solid conclusions cannot be drawn, all these cell subsets have key roles in the pathophysiology of GVHD [44] and thus might have contributed to the increased risk of GVHD in patients who received post-transplantation Len. Taking into account the currently available data on the use of pomalidomide in GVHD treatment [33], perhaps it would be a better option to avoid GVHD flares under treatment with Len. Furthermore, this approach also would allow the use of IMiDs in patients previously refractory to Len. This concept warrants prospective evaluation.

In the present EMN-II trial, the CuI of aGVHD at 100 days was 39% for grade II-IV and 21.7% for grade III-IV. In the EMN-I trial, in which Bz was combined with tacrolimus and rapamycin for GVHD prophylaxis, these CuIs were 35% and 10%, respectively. Thus, the CuI of grade II-IV was similar in the 2 studies, but that of grade III-IV aGVHD was higher in the present study. It could be hypothesized that in the previous trial, Bz was combined with tacrolimus and sirolimus, whereas in the present trial, it was combined with tacrolimus and MTX. Thus, the combination of Bz with sirolimus instead of MTX might increase the efficacy of Bz for GVHD prophylaxis, as we previously described in a preclinical model [45], although the number of patients in both studies is too small to draw any solid conclusions. Other studies have described the efficacy of Bz in GVHD prophylaxis with similar results in terms of grade II-IV aGVHD but with a lower risk of grade III-IV aGVHD compared with the present trial [46,47].

In conclusion, combinations of new drugs with alloSCT could have a synergistic effect and improve outcomes in HR MM patients. In this trial, the use of Bz in the conditioning regimen was safe and associated with a high response rate after alloSCT. Maintenance therapy with Bz and Len is feasible and could contribute to decreasing relapse post-transplantation. Adherence to maintenance after transplantation might be hampered by toxicity, which should be investigated in future RCTs.

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Conflict of interest statement: M.R.S. has received honoraria derived from lectures from Janssen and Celgene/BMS. T.C.V. has consulted for Celgene/BMS. F.P. has collaborated on advisory boards for Janssen and Celgene/BMS. H.E. has served in a consulting or advisory role for Janssen, Amgen, Celgene/BMS, Takeda, Sanofi, GSK, and Novartis and has received honoraria from Janssen, Amgen, Celgene/BMS, Takeda, Sanofi, GSK, and Novartis and research funding from Janssen, Amgen, Celgene/BMS, Sanofi, and GSK. H.N. has been employed by and is a shareholder in Genmab. J.L.R. has received honoraria derived from lectures from Janssen. J.A.P.S. has collaborated in educational activities and/or advisory board and/or support of research projects from Janssen, Celgene/ BMS, Novartis, Jazz, Takeda, Gilead, Amgen, AbbVie, and Alexion. G.G. has served as an advisor to Fujimoto Pharmaceutical, has received honoraria from Bristol Myers Squibb, and in a shareholder in XNK Therapeutics and Astra Zeneca. The other authors have no conflicts of interest to disclose.

Authorship statement: J.A.P.S. designed and directed the study. M.R.S. performed the data analysis and interpretation, drafted the manuscript ,and designed the figures and tables. All authors had substantial contributions to the conception of the work, contributed to the patient enrollment, and provided patient care and protocol-directed procedure implementation. All authors discussed the results and commented on the manuscript and approved the final manuscript for publication. J.A.P.S. supervised the final version of the manuscript.

Data sharing statement: For original data requests, please contact josea.perez.simon.sspa@juntadeandalucia.es.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.01.026.

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