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Response to Novel Drugs before and after Allogeneic Stem Cell Transplantation in Patients with Relapsed Multiple Myeloma

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A B S T R A C T

Multiple myeloma (MM) remains as an incurable disease and, although allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative approach, most patients ultimately relapse, and their treatment remains challenging. Because allo-HSCT can modify not only the biology of the disease, but also the immune system and the microenvironment, it can potentially enhance the response to rescue therapies. Information on the efficacy and safety of novel drugs in patients relapsing after allo-HSCT is lacking, however. The objectives of this study were to evaluate the efficacy and toxicity of rescue therapies in patients with MM who relapsed after allo-HSCT, as well as to compare their efficacy before and after allo-HSCT. This retrospective multicenter study included 126 consecutive patients with MM who underwent allo-HSCT between 2000 and 2013 at 8 Spanish centers. All patients engrafted. The incidence of grade II-IV acute graft-versus-host disease (GVHD) was 47%, and nonrelapse mortality within the first 100 days post-transplantation was 13%. After a median follow-up of 92 months, overall survival (OS) was 51% at 2 years and 43% at 5 years. The median progression-free survival after allo-HSCT was 7 months, whereas the median OS after relapse was 33 months. Patients relapsing in the first 6 months after transplantation had a dismal prognosis compared with those who relapsed later (median OS, 11 months versus 120 months; $P < .001$). The absence of chronic GVHD was associated with reduced OS after relapse (hazard ratio, 3.44; $P < .001$). Most patients responded to rescue therapies, including proteasome inhibitors (PIs; 62%) and immunomodulatory drugs (IMiDs; 77%), with a good toxicity profile. An in-depth evaluation, including the type and intensity of PI- and IMiD-based combinations used before and after allo-HSCT, showed that the overall response rate and duration of response after allo-HSCT were similar to those seen in the pretransplantation period. Patients with MM who relapse after allo-HSCT should be considered candidates for therapy with new drugs, which can achieve similar response rates with similar durability as seen in the pretransplantation period. This pattern does not follow the usual course of the disease outside the transplantation setting, where response rates and time to progression decreases with each consecutive line of treatment.

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INTRODUCTION

Multiple myeloma (MM) is a neoplastic plasma cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow and the presence of a monoclonal protein in the blood and/or urine, resulting in myeloma-defining events. The outcomes of patients with MM have improved significantly due to the introduction of novel agents in both the relapse and upfront settings; however, the disease remains incurable for most patients. The role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in treating MM remains challenging, because although it is a potentially curative approach [1–4], the associated high toxicity and relapse rate are important concerns. In this regard, the International Myeloma Working Group together with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation (EBMT) have agreed that allo-HSCT should be considered an appropriate therapy for all eligible patients with early relapse (occurring within 24 months) after primary therapy that included autologous stem cell transplantation (ASCT) and/or high-risk features, while acknowledging that prospective randomized trials are needed to define the role of allo-HSCT in patients who relapse after primary therapy for MM [5].

Allo-HSCT offers a graft-versus-myeloma effect that may be agnostic to cytogenetic risk. The unacceptably high morbidity and nonrelapse mortality (NRM), related at least in part to the use of myeloablative conditioning regimens [6–9], have resulted in a shift toward reduced-intensity conditioning (allo-RIC) regimens [10–16]. Despite this, the decision to proceed to allo-HSCT is increasingly challenging with the advent of new therapies. However, although the role of allo-HSCT is a subject of intense debate, survey studies by the EBMT have shown an increasing number of patients undergoing allo-HSCT for MM [17], and in fact, the use of novel drugs does not appear to have impacted the rate of transplantation [18].

Despite the high response rate and the reduced NRM observed in the years after the advent of allo-RIC regimens, most patients ultimately relapse. Thus, relapse and progression are the main causes of treatment failure. Treatment of patients who relapse after allo-HSCT remains a challenge. Until recently, these patients have not been considered candidates for treatment with experimental drugs, based mainly on concerns regarding the toxicity profile of these drugs in the transplantation setting. Moreover, most of the recent trials that have led to the approval of new drugs excluded allo-HSCT recipients, and thus these drugs' efficacy has not been appropriately evaluated in this setting. Several small studies have been reported describing the efficacy of proteasome inhibitors (PIs) or immunomodulatory drugs (IMiDs) with or without concomitant donor lymphocyte infusion (DLI) as salvage therapy after allo-HSCT [19–23], but none of these has compared the efficacy achieved after allo-HSCT with that obtained pretransplantation with similar combinations. It is well known that the outcomes of patients with MM follows a pattern in which the response rate decreases and the median duration of response decreases after each consecutive line of therapy, a process that ultimately leads to treatment failure and death [24]. Whether or not this concept applies to relapse after allo-HSCT has not been evaluated, and considering the changes to the immune system and microenvironment induced by the allograft, this scenario might represent a good opportunity to evaluate the efficacy of novel agents before and after transplantation.

The present study evaluated the outcomes of a series of 126 patients with MM who underwent allo-HSCT. After a median follow-up of 92 months, overall survival (OS) was 51% at 2 years and 43% at 5 years, with 10% of patients alive at longer than 10 years beyond transplantation. The median OS after relapse was 33 months. Most patients responded to rescue therapy including PIs (62%) and IMiDs (77%) with good tolerability. Moreover, this is the first study to compare the efficacy and toxicity of novel drug/novel combinations before and after allo-HSCT, and we show that they can be safely used and that the response rate and duration of response are similar to those observed in the pretransplantation setting, indicating that allo-HSCT can potentially sensitize myelomatous plasma cells, modifying the usual course of MM.

METHODS

Patients

We report a retrospective multicenter analysis of 126 consecutive patients with MM who underwent allo-HSCT between January 2000 and December 2013 at 8 Spanish centers. The institutional Ethics Committees of all participating centers approved the study, and all patients provided written informed consent before entering the study in accordance with the Declaration of Helsinki. All but 2 procedures were done as routine clinical practice outside of an investigational clinical trial.

Disease Response and Definitions

Response to treatment and progression were determined according to the criteria formulated by the International Myeloma Working Group [25]. Complete response (CR) was defined as negative immunofixation in serum and urine and <5% plasma cells in bone marrow aspirate, including the disappearance of any soft tissue plasmacytoma. Progression-free survival (PFS) was defined as the time from allo-HSCT to the date of progression or death from any cause or last follow-up. Patients alive without progression at their last follow-up were censored. OS was defined as the time from allo-HSCT to the date of death or last follow-up. Patients alive at their last follow-up were censored. OS after relapse was defined as the time from relapse after allo-HSCT to the date of death or last follow-up. NRM was defined as death without previous occurrence of relapse or progression. Relapse incidence (RI) was calculated from the date of allo-HSCT to the date of relapse or progression. NRM and RI were considered competing events.

Deaths due to infection (bacterial, fungal, or viral) in the context of active graft-versus-host disease (GVHD) were considered related to GVHD. Acute GVHD (aGVHD) was defined as grade II-IV according to the Seattle criteria [26]. Chronic GVHD (cGHVD) was defined as mild, moderate, or severe according to National Institutes of Health 2005 criteria [27]. Patients who had evidence of engraftment were evaluable for aGVHD, whereas patients who engrafted and survived longer than 100 days after allo-HSCT were evaluable for cGVHD, with death or progression/relapse without cGVHD as competing events.

Statistical Analysis

The co-primary endpoints of this study were (1) to evaluate the efficacy and safety of rescue regimens based on PIs and IMiDs in patients with MM who relapsed after allo-HSCT and (2) to compare the efficacy after allo-HSCT with that observed before allo-HSCT for the same patients treated with similar combinations before and after transplantation. Secondary endpoints included the efficacy of allo-HSCT in terms of response and RI, PFS, and OS. The incidences of aGVHD and cGVHD were also analyzed.

All nominal and continuous characteristics were described the usual tables and indexes; comparisons were done using standard nonparametric tests, including the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney *U*test for continuous variables. Survival curves were estimated using the Kaplan-Meier method, with group comparison using the log-rank test. Prognostic factors for OS after relapse were analyzed for statistical significance using the Cox proportional hazards model. Factors that showed a significance of $P < .10$ were included in a multivariate Cox regression model: age, number of lines before allo-HSCT, extramedullary disease at allo-HSCT, extramedullary disease at relapse, aGVHD, and cGVHD. The probabilities of disease progression and GVHD were calculated using cumulative incidence estimates. NRM and RI were analyzed and compared using Gray's test. Cumulative incidence was computed with the cmprsk package for R version 2.14.0 (R Institute for Statistical Computing, Vienna, Austria), and other analyses were performed using SPSS 19.0 (IBM, Armonk, NY).

RESULTS

Patient Characteristics, Conditioning Regimens, and GVHD Prophylaxis

Baseline and transplantation characteristics of the 126 patients with MM who underwent allo-HSCT between January 2000 and December 2013 are summarized in Table 1. The median duration of follow-up for surviving patients was 92 months (range, 22 to 197 months). In the pretransplantion period, 71 patients (56%) had been treated with a PI-containing regimen and 48 (38%) had received an ImiD-containing regimen. Thirty-six patients (28.5%) received both agents. Details of the PI- and ImiD-based regimens are provided in Table 2.

Table 1
Baseline Patient and Transplantation Characteristics (N = 126)

Characteristic	Value
Age, yr, median (range)	52 (22-66)
Male sex, n (%)	78 (62)
IgG/IgA/Bence Jones/nonsecretory, n (%)	68 (54)/23 (18)/31 (25)/4 (3)
ISS I/II/III, n (%)*	20 (28)/26 (37)/25 (35)
High cytogenetic risk: (t(4;14), t (14;16), or 17p del), n (%)†	19 (29)
Number of treatment lines before allo-HSCT, median (range)	3 (1-9)
1, n (%)	33 (26.2)
2-3, n (%)	62 (49.2)
>3, n (%)	31 (24.6)
PIs, n (%)	71 (56)
IMiDs, n (%)	48 (38)
Previous ASCT, n (%)	105 (83)
Time between diagnosis and allo-HSCT	30 (8-130)
Allo-HSCT indication, n (%)	
First response	15 (12)
Sensitive relapse	66 (52.3)
Refractory disease	45 (35.7)
Disease status at allo-HSCT, n (%)‡	
CR	16 (13)
VGPR/PR	86 (68)
Stable/progressive disease	22 (19)
Extramedullary disease at allo-HSCT, n (%)	35 (28)
Reduced-intensity conditioning, n (%)	111 (89)
Conditioning regimen, n (%)	
Fludarabine 150 mg/m^2/melphalan 140 mg/m^2	60 (48)
Fludarabine 90 mg/m^2/TBI 2 Gy	16 (13)
Fludarabine/melphalan/bortezomib	11 (9)
T cell depletion	20 (16)
Others	19 (14)
Unrelated donor/HLA-matched (10/10)	24 (19)/11 (91)
Peripheral blood stem cell source	111 (89)
CD34$^+$ cells infused per kg, $\times 10^6$, median (range)	4.8 (.5-14.2)
GVHD prophylaxis, n (%)	
Calcineurin inhibitor + methotrexate	65 (56)
Cyclosporine A + mycophenolate mofetil	28 (23)
Others	33 (26)
Follow-up post-allo-HSCT, mo, median (range)	92 (22-197)

ISS indicates Injury Severity Score; VGPR, very good partial response.
* ISS data available for 71 patients.
† Fluorescein in situ hybridization data available for 65 patients.
‡ Disease status at allo-HSCT available for 124 patients.

Engraftment, GVHD, and NRM

All 126 patients engrafted. The incidence of grade II-IV aGVHD was 47% (grade III-IV, 22%) and the 3-year cumulative incidence of cGVHD was 51% (moderate, 14%; severe, 12%). NRM within the first 100 days post-transplantation was 13%, whereas the global NRM at any time was 31.7%. More information is provided in Table 3.

Overall Outcomes after Transplantation

The overall response rate (ORR) after allo-HSCT was 74%, with 56% of patients achieving CR. At day +100 after transplantation, 82 patients (84.5%) either remained stable or showed improved disease status compared with their status at transplantation, including 13 patients with progressive or stable disease at transplantation. Seventy-five patients (59.5%) relapsed after allo-HSCT, 57 of them with extramedullary involvement, with a median time to relapse or progression of 8 months post-transplantation (range, 1 to 141 months). The cumulative incidences of NRM and relapse after allo-HCT are shown in Figure 1.

After a median follow-up of 92 months for surviving patients (range, 22 to 197 months), 85 patients (67.4%) died, 44 due to relapse or progression and 40 due to NRM. PFS was 24% at 2 years and 18% at 5 years, with a median PFS of 7 months (Figure 2).

Remarkably, even among patients who relapsed after allo-HSCT, time to relapse discriminates subgroups of patients with very different outcomes: patients who relapse <6 months, 6 to 24 months, and >24 months after transplant have a median OS of 11 months, 68 months and not reached, respectively ($P < .001$). Moreover, 83% of patients who relapsed at 12 months after transplantation were still alive at 5 years after allo-HSCT, with a median OS not reached.

Evaluation of New Drug Efficacy before and after Allo-HSCT in All Patients

Seventy-one patients (56%) received threatment with PIs in the pretransplantation period, and 35 (27.7%) did so in the post-transplantation period. The ORR after treatment with a PI-based scheme was superior in the pretransplantation period than in the post-transplantation period (76% versus 65.7%; $P > .05$), with a longer time to progression (TTP) (13 months versus 7 months; $P > .05$), although these differences did not reach statistical significance. However, an in-depth evaluation (Table 2) shows that the PI-based schemes used in the pretransplantation period were more intensive than those used in the post-transplantation period, including ASCT with or without maintenance in 21% of patients (n = 15) and high-intensity combination chemotherapy regimens (VDLPACE/VDTPACE) in 15% (n = 11), whereas the majority of patients treated with PIs post-HSCT received PI in monotherapy with or without steroids (n = 21; 60%). Comparing response to PIs including equivalent schemes in terms of intensity (Table 2), the ORR to bortezomib with or without steroids was higher in the pretransplantation period than in the post-transplantation period (79% versus 62%; $P > .05$), but similar when mono/polychemotherapy was added (60% versus 63%; $P > .05$). In addition, 4 out of 5 patients responded to bortezomib plus panobinostat, and 1 patient responded to carfilzomib in the post allo-HSCT.

Table 2
New Drugs before and after Allo-HSCT

Drug	Pre-HSCT	Post-HSCT
PIs (any regimen)	N = 71	N = 35
ORR, % (n/N)	76 (52/71)	65.7 (23/35)
CR	21	19
PR	55	44
<PR	24	35
TTR, mo, median (range)	3 (1-10)	4 (1-9)
TTP, mo, median (range)	13 (1-108)	7 (1-132)
Scheme responses, ORR, % (n/N)		
Bortezomib ± steroids	79 (19/24)	62 (13/21)
Bortezomib + mono/polychemotherapy ± steroids	60 (9/15)	63.6 (7/11)
VDLPACE/VDTPACE	82 (9/11)	-
Bortezomib combination + ASCT ± maintenance	100 (15/15)	-
IMiDs (any regimen)	N = 48	N = 33
ORR	75 (36/48)	76 (26/33)
CR	10	8
PR	65	68
<PR	25	24
TTR, mo, median (range)	4 (2-8)	4 (1-14)
TTP, mo, median (range)	7 (2-31)	10.5 (1-38)
Scheme responses, ORR, % (n/N)		
Thalidomide ± steroids	80 (4/5)	80 (4/5)
Thalidomide + mono/polychemotherapy ± steroids	72.7 (8/11)	77.7 (7/9)
Lenalidomide ± steroids	91.6 (11/12)	72 (8/12)
Lenalidomide + mono/polychemotherapy ± steroids	—	75 (3/4)
VDLPACE/VDTPACE	82 (9/11)	—
IMiD combination + ASCT ± maintenance	100 (3/3)	—
PI-IMiD combinations, ORR, % (n/N)		
Bortezomib + IMiD ± steroids	33.3 (1/3)	85.7 (6/7)
Thalidomide + bortezomib ± steroids	0 (0/1)	100 (1/1)
Lenalidomide + bortezomib ± steroids	100 (1/1)	80 (4/5)
Pomalidomide + bortezomib ± steroids	100 (1/1)	100 (1/1)
Second-generation new drugs, ORR, % (n/N)		
Bortezomib + panobinostat ± steroids	0 (0/1)	80 (4/5)
Carflizomib ± steroids	—	100 (1/1)
Thalidomide + elotuzumab ± steroids	0 (0/2)	—
Lenalidomide + panobinostat ± steroids	—	100 (1/1)
Lenalidomide + elotuzumab ± steroids	—	100 (1/1)
Pomalidomide ± steroids	100 (1/1)	100 (4/4)

TTR indicates time to response; VDLPACE, bortezomib + dexamethasone + lenalidomide + adriamycin + cyclophosphamide + etoposide; VDTPACE, bortezomib + dexamethasone + thalidomide + adriamycin + cyclophosphamide + etoposide.

Forty-eight patients (38%) received IMiDs in the pretransplantation period, and 33 (26%) did so in the post-transplantation period. The ORR to IMiD-containing regimens was comparable in the post-transplantation and pretransplantation periods (75% versus 76%; $P = .50$), but again, the regimens used in the pretransplantation period were more intensive than those used in the post-transplantation period, including ASCT with or without maintenance in 6.25% (n = 3) and high-intensity combination chemotherapy regimens (VDTPACE/VDLPACE) in 23% (n = 11) (Table 2). Comparing responses to IMiDs within equivalent schemes (Table 2), response rates were not significantly different for thalidomide combinations, although the ORR to lenalidomide with or without steroids was higher in the pretransplantation period compared with the post-transplantation period (91% versus 72%; $P > .05$). Of note, all 4 patients who received post-allo-HSCT pomalidomide with or without steroids responded, as did the 2 patients who received IMiDs plus elotuzumab or panobinostat. Interestingly, TTP was significantly superior (7 months versus 10.5 months; $P = .04$) in patients who received IMiDs within the post-allo-HSCT setting, despite the fact that the regimens were less intensive.

In addition, 3 patients received PI plus IMiD combination therapy in the pretransplantation period and 7 did so in the post-transplantation period, with superior ORR in the post-translpantation transplantation period (85.7% versus 66.6%; $P > .05$) (Table 2).

OS was 60% at 1 year after relapse and 53% at 2 years after relapse, with a median OS after relapse of 33 months (range, 13 to 53 months) (Figure 3). In a multivariable model, the absence of cGVHD was the most significant factor associated with reduced OS after relapse (hazard ratio [HR], 3.48; 95% confidence interval [CI], 1.6 to 7.1; $P = .001$). In addition, less pretreated patients (ie, number of lines before allo-HSCT, 1 versus 2/3 versus ≥4) had better OS after relapse (HR, .41; 95% CI, .08 to .68), just like absence of grade III-IV aGVHD had a (HR, .29; 95% CI, 01-06; $P < .01$).

Table 3
Engraftment, GVHD, and NRM (N = 126)

Variable	Value
Engraftment	126 (100)
Time to neutrophils >.5 × 10^9/L, d, median (range)	16 (6-27)
Time to platelets >20 × 10^9/L, d, median (range)	11 (0-18)
aGVHD, n (%)	68 (57)
Grade II-IV	59 (47)
Grade III-IV	28 (22)
cGVHD at 3 yr, n (%)	64 (51)
Mild, moderate, severe, unknown	11 (9)/13 (10)/11 (9)/29 (23)
NRM, n (%)	
At day +100	17 (13)
Global	40 (31.8)
Causes of death, n (%)	
GVHD	17 (42.5)
Infections not related to GVHD	15 (37.5)
Post-transplantation lymphoproliferative disorder	2 (5)
Pulmonary toxicity	1 (2.5)
Pulmonary hemorrhage	1 (2.5)
Sinusoidal obstruction syndrome	1 (2.5)
Other causes	3 (7.5)

Evaluation of New Drug Efficacy before and after Allo-HCST in Patients Receiving the Same Drug before and after Allo-HSCT

To further compare drug sensitivity before and after allo-HSCT, we next focused only on those patients receiving PIs and/or IMiDs before allo-HSCT and the same drug after transplantation and compared the responses in the same patient before and after allo-HSCT. Eighteen out of 75 patients who relapsed after allo-HSCT had received a PI-based regimen in both the pretransplantation and post-transplantation periods. Fifteen of these 18 patients achieved at least a partial response (PR) (CR, n = 6) before transplantation, and 11 of these 15 patients responded again when they received PIs after allo-HSCT (CR, n = 3). Moreover, 2 of the 3 patients who were refractory to PIs before allo-HSCT responded when PIs were used as salvage therapy after HSCT. Finally, 5 patients who did not respond to PIs in the post-transplantation period achieved stable disease, with TTP between 4 and 8 months.

In contrast, 12 out of 75 patients who relapsed after allo-HSCT received IMiDs in both the pretransplantation and post-transplantation periods. Ten of these 12 patients achieved at least PR pretransplantation (CR, n = 3) and, when they were retreated post-allo-HSCT, 7 responded again to IMiDs (CR, n = 2). Moreover, 2 patients who were refractory before allo-HSCT responded to IMiDs post-transplantation. Finally, 2 of 3 patients who were refractory to IMiDs in the post-transplantation period achieved stable disease, with a TTP of 8 months in one and 13 months in the other.

Remarkably, in the group of patients who responded to either PIs or IMiDs in both the pretransplantation and post-transplantation periods, the time to response and TTP were equivalent, even though the regimens were significantly more intensive in the pretransplantation period. Outcomes and treatment responses of patients who received PIs and IMiDs in both the pretransplantation and post-transplantation periods are summarized in Table 4.

Toxicity of PIs and IMiDs after Allo-HSCT

Regarding salvage treatment toxicity, 14 of 33 patients treated with IMiDs had a previous history of aGVHD, and 15 had a previous history of cGVHD. GVHD reactivation was reported in 2 patients, both of whom were treated with a lenalidomide-based regimen. One patient with a previous history of aGVHD and cGHVD developed late aGVHD after 3 cycles of lenalidomide plus prednisone with skin involvement, and another patient with a previous history of cGVHD developed a new episode of

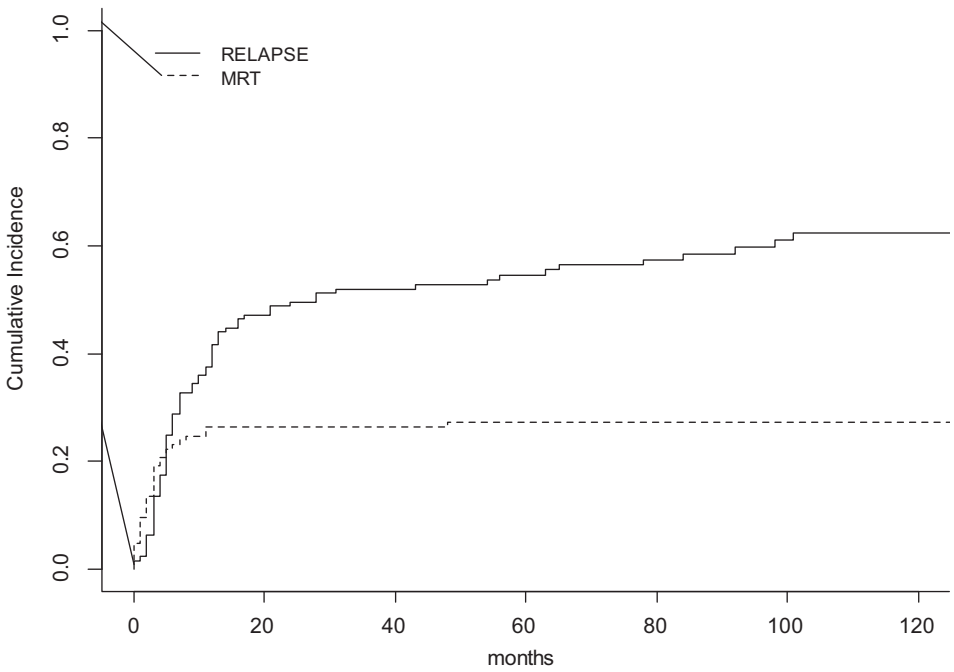

Figure 1. Cumulative incidences of NRM and relapse after allo-HSCT.

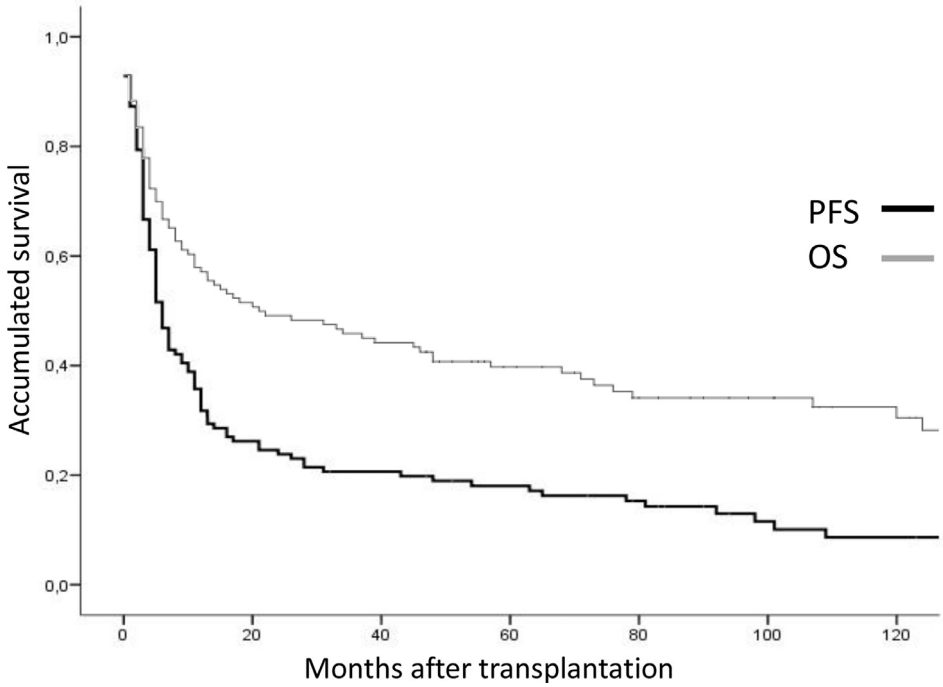

Figure 2. PFS and OS.

moderate cGHVD with lichenoid mouth and ocular involvement after 2 cycles of lenalidomide plus prednisone. In contrast, 19 of 35 patients treated with PIs had a history of previous aGVHD, and 17 had a history of previous cGVHD. No GVHD flares were reported. In addition, 2 patients developed grade 2 liver toxicity, and 4 patients developed grade 3-4 peripheral neuropathy; only 1 patient needed to discontinue bortezomib.

Hematologic toxicity was reported in 6 patients and was related to low neutrophil and platelet counts (thrombocytopenia and neutropenia in 4 patients and grade 2 thrombocytopenia in 2 patients.

DISCUSSION

Allo-HSCT is usually relegated to advanced lines of treatment based on the assumption that once relapse has occurred after transplantation, no other rescue therapy is appropriate for these patients, due to either ineffectiveness or toxicity. Nevertheless, the present study, as well as several previous studies, have challenged this concept. Based on findings reported by the EBMT [13], OS from the time of first relapse/progression was superior in patients treated with ASCT/allo-RIC compared with patients treated with ASCT alone (50% versus 27% at 60 months; $P = .003$). The same finding was recently reported by the Center of International Blood and Marrow Transplant Research; although both cohorts (ASCT/ASCT and ASCT/allo-HSCT) had a similar risk of death in the first year after relapse (HR, .72; $P = .12$), the ASCT/allo-HSCT group had superior OS (HR for death in ASCT/ASCT, 1.55; $P = .0052$) beyond 12 months after relapse [28]. This observation might reflect the fact that allo-HSCT can modify the biology of the disease, directly targeting the myelomatous plasma cells as well as the microenvironment, and the well-documented graft-versus-myeloma effect induced by reactive allogeneic T cells may persist after relapse and contribute to an enhanced disease response [29,30]. In line with this observation, our analysis showed that the presence of cGVHD was the most important favorable factor predicting OS not only after transplantation, but also after relapse. In this regard, the immune profile of patients with MM has been characterized in detail, and immune exhaustion, including such abnormalities as a significant increment of TCR-$\gamma\delta^+$ T lymphocytes and Tregs, altered distribution of BDCA-1^+ myeloid dendritic cells and tissue macrophages, and down-regulation of activation markers in T lymphocytes, have been noted, all of which have been correlated with a poorer outcomes outside of the transplantation setting [31].

Accordingly, even after disease relapse, allo-HSCT might represent an appropriate platform for the use of rescue treatments based on novel drugs. Unfortunately, most of the recent trials that have led to the approval of new drugs excluded allo-HSCT recipients, and thus their efficacy has not been appropriately evaluated in this setting. Moreover, neither the EBMT nor the Center of International Blood and Marrow Transplant Research retrospective study, in which the effects of new drugs as salvage therapy after allo-HSCT were analyzed, compared the efficacy of these drugs with that seen in the pretransplantation setting. Thus, Coman et al [19] evaluated the efficacy of lenalidomide with or without dexamethasone in 52 patients who relapsed after allo-RIC and reported an ORR of 83%, including 29% in CR. Of note, the development of GVHD was associated with the response rate [19]. Similarly, Minnema et al [20] administered lenalidomide with or without dexamethasone to 13 patients who relapsed after allo-HSCT. The ORR was 46% for lenalidomide alone and was increased to 87.5% with a combination of lenalidomide and dexamethasone. Bensinger et al [23] evaluated the response to and tolerability of lenalidomide monotherapy in 18 patients with MM who progressed or relapsed after allo-HSCT. In their study, lenalidomide resulted in extended disease control (>12 months) in 50% of patients. Montefusco et al [21] reported a PFS of 31% and OS of 73% using the combination of bortezomib/dexamethasone plus DLI in patients with relapsed MM. El Cheikh et al [22] treated 37 patients with progressive or residual disease after allo-RIC using bortezomib with (n = 26) or without (n = 11)

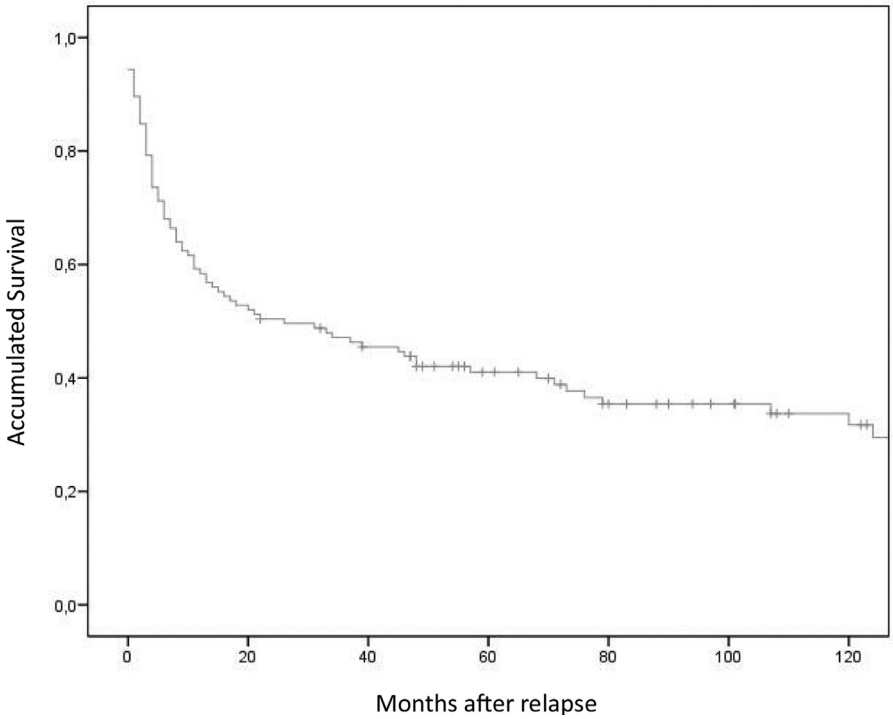

Figure 3. OS after relapse.

dexamethasone and achieved am ORR of 73% with 65% OS at 18 months [22].

In our study, most patients responded to rescue therapies including IMiDs (76%) and PIs (65.7%), in agreement with published data. In addition, we had the opportunity to evaluate the efficacy of different drug combinations used in the same patient before and after allo-HSCT, representing a unique opportunity to evaluate whether or not allo-HSCT modifies drug sensitivity in relapsed patients and, to the best of our knowledge, the first study to evaluate drug sensitivity to the same drug in the same patient both before and after allo-HSCT. Interestingly, we observed that efficacy, in terms of response rate and duration of response, was at least similar to that observed in the pretransplantation setting. Moreover, 4 patients who were refractory to PIs (n = 2) or IMiDs (n = 2) before allo-HSCT responded when PIs or IMiDs were used again as salvage therapy after allo-HSCT, and 7 of 9 patients who did not respond to these agents after allo-HSCT achieved stable disease, with TTP between 4 and 13 months.

In addition, information is scanty regarding the safety of novel drugs used as rescue therapy after allo-HSCT. In this regard, Coman et al [19] reported that 31% of patients developed new or exacerbated aGVHD after lenalidomide treatment as salvage therapy post-HSCT. In line with this observation, Minnema et al [20] reported aGVHD in 5 out of 13 patients who received lenalidomide as a single agent after allo-HSCT, and Bensinger et al [23] reported that 2 out of 18 patients who received lenalidomide monotherapy died due to GVHD. In our retrospective study, only 2 out of the 24 patients treated with a lenalidomide-based regimen developed GVHD. Dose, timing, and concomitant medications should be considered to explain these differences. On the other hand, PIs seem to be safe for patients with MM relapsing or progressing after allo-HSCT, without unexpected organ toxicities in a prospective phase II trial reported by Monefusco et al [21], while El-Cheickh et al [22] reported no worsening of GVHD symptoms in patients treated with bortezomib. In our series, none of the patients who received PIs post-HSCT developed GVHD, and only 1 out of the 33 patients with MM discontinued bortezomib treatment due to grade 3 neuropathy. Moreover, overall, our study shows that both the hematologic and nonhematologic toxicity profile observed with PIs and/or IMiDs post-HSCT is not significantly different from that reported outside the allo-HSCT setting. The retrospective nature of the present study should be emphasized to carefully consider this toxicity profile, and prospective studies are needed to confirm these data.

Although the role of allo-HSCT is controversial in MM, and its use in the current era remains a topic of debate, it is worth mentioning that even in this series of patients who relapsed after allo-HSCT, long-term survival could be achieved. This was especially true for patients who relapsed between 6 and 24 months after transplantation or at >24 months after transplantation, in whom the median OS was 68 months and not reached, respectively. Moreover, 83% of patients who relapsed at 12 months after transplantation were still alive at 5 years after allo-HSCT, with a median OS not reached. Thus, for very high-risk patients, allo-HCT could be considered as a platform for additional therapeutic strategies.

Our study is the first to compare the efficacy and toxicity of novel drugs before and after allo-HSCT, and our findings show that they can be used safely; moreover, the new immune system may enhance the activity of these agents. Therefore, patients with MM who relapse after allo-HSCT should be considered candidates for receipt of novel agents, which are safe and allow for response rates in a similar proportion of patients and with similar durability as in the pretransplantation period. This pattern does not reproduce the usual course of the disease, in which response rates and TTP decrease with consecutive lines of treatment, suggesting that the new immune system may contribute to the enhanced efficacy of novel drugs.

Table 4
Outcomes of Patients Treated with PIs and/or IMiDs in Both in the Pre- and Post-Allo-HSCT Settings (N = 23)

	Pre-Allo-HSCT				Post-Allo-HSCT				
Patient	PIs/IMiDs Schemes (Line of Treatment)	Response	TTR, mo	TTP, mo	IPs/IMiDs Schemes	Response	TTR, mo	TTP, mo	Comments
1*	Bz + polychemotherapy x 4 (2ª)	PD	-	-	**Bz + Len + Pre**d x 10 (1ª)	Stringent CR	6	60	No grade 3-4 toxicity. Severe cGVHD after DLI. Dead 5 yr after relapse
	VDTPACE x 2 (4ª)	PR7	2	-					
2*	Bz/CC x 6 + ASCT (1ª)	VGPR	3	16	**Thal x 8** (1°)	VGPR	2	10	No grade 3-4 toxicity. Dead 4 yrs after relapse
	Len + Dx x 9 (2ª)	PR	4	11	Thal + CFM + Dx x 7 (2°)	CR	4	12	
	Bz + LBH + Dx x 4 (3ª)	SD	-	6	**Bz x 4** (3°)	SD	-	6	
	VDLPACE x 3 (5°)	PR	3	-	Bz + Poma + Pred x 6 (4°)	SD	-	8	
3	**Bz + Dx** x 3 (2ª)	SD	-	2	**Thal + CFM + Pred** x 7 (1°)	SD	-	13	Grade 3 thrombocytopenia. Alive 44 months after relapse
	PAD x 2 (3ª)	SD	-	2	**Ben + Bz + Dx** x 6 (2ª)	PR	4	12	
	Len + Dx x 4 (4ª)	PR	4	2					
	Thal + CFM + Dx x 8 (5ª)	PR	5	-					
4*	**Thal + Dx** x 12 (1ª)	CR	6	24	**Bz** x 7 (1ª)	CR	6	10	No grade 3-4 toxicity. Dead 4 years after relapse
	Bz + Dx x 5 (3ª)	VGPR	4	-	**Len + Pred** x 8 (2ª)	PR	2	10	
5*	Thal/Dx x 5 + ASCT	CR	7	16	**Bz + Dx** x 7	PR	3	7	No grade 3-4 toxicity. Alive 38 months after relapse
	Bz/Dx x 6 + ASCT	CR	4	6	**Len + Dx** x 8	PR	4	12	
	Len + Dx x 10	CR	9	-	Len + CFM x 9	PR	6	11	
					Bz + Poma + Dx	PR	9	-	
6*	**Bz/Dx** x 6 + ASCT (1ª)	CR	3	24	**Bz + Len + Dx** x 11 (1ª)	PR	7	-	No grade 3-4 toxicity. Alive 54 months after relapse
7*	**Bz + Dx** x 5 (2ª)	CR	4	NA	**Bz + CFM** x 6 (1ª)	CR	3	7	No grade 3-4 toxicity. Alive 12 months after relapse
					Len + Dx x 6 (2ª)	PR	5	-	
8*	**Bz + Dx** x 6 (2ª)	VGPR	3	NA	**Bz + Dx** x 7 (1ª)	PR	3	8	No grade 3-4 toxicity. Dead 3 years after relapse
					Len + Dx x 11 (2ª)	PR	6	12	
9*	**Bz + CFM + Dx** x 7 (2ª)	PR	2	NA	**Bz** x 6 (1ª)	SD		6	Grade 3 thrombocytopenia. Dead 2.5 years after relapse
					Thal x 6 (2ª)	PR	2	4	
					Thal + CFM + Dx x 5 (3ª)	PR	2	4	
10*	**Bz + CFM + Dx** x 4 (2ª)	PR	2	NA	**Bz +Thal+Dx** x 2 (3ª)	SD	-	4	Grade 3 thrombocytopenia. Dead 5 months after relapse
11*	Bz/Dx x 6 + ASCT (1ª)	CR	4	108	Len + Dx x 9 (2ª)	PR	8	16	No grade 3-4 toxicity. Mild cGVHD after Len. Alive 28 months after relapse
	Bz + Dx x 7 (2ª)	PR	4	-	**Bz + CFM** x 8 (3ª)	PR	3	7	
12*	Thal + CFM + Dx (2ª)	PR	4	7	**Bz** (2ª)	PR	4	7	No grade 3-4 toxicity. Poor performance status at relapse. Died 1 year after relapse
	Bz + Dx (3ª)	CR	3	18					
	Len + Dx (4ª)	PR	4	2					
	PAD (5ª)	PR	3	-					
13*	Bz/Dx + ASCT (1ª)	CR	3	18	**Bz + chemo** (1ª)	PD	-	2	No grade 3-4 toxicity. Very poor performance status at transplant. Dead 4 months after transplant
	Len + Dx (2ª)	PR	4	3					
	Bz + Len + Dx (4°)	SD	-	5					
	VDTPACE (5ª)	PD	-	1					
14	**Bz + Dx** (1ª)	PR	2	5	**Bz + Mel + Pred** (2ª)	PR	2	8	No grade 3-4 toxicity. Dead 18 months after relapse

(*continued*)

Table 4 (*Continued*)

	Pre-Allo-HSCT				Post-Allo-HSCT				
Patient	PIs/IMiDs	Response	TTR, mo	TTP, mo	IPs/IMiDs	Response	TTR, mo	TTP, mo	Comments
	Schemes (Line of Treatment)				Schemes				
							-		
15*	**Bz + Dx** x 4 (2ª)	PR	5	-	**Bz** (1ª)	SD	-	6	No grade 3-4 toxicity. Dead 144 months after relapse
					Bz + LBH + Dx (3ª)	SD	-	4	
					Thal + CFM + Dx (4ª)	SD	-	4	
					Len + Dx (6ª)	SD	-	8	
					Thal + Elo + Dx (7ª)	SD		4	
16*	**Thal + CFM + Dx** x 6 (2ª)	CR	3	NA	**Bz** x 7 (2ª)	PR	3	8	No grade 3-4 toxicity. Dead 144 months after relapse
	Bz + Dx x 2 (3ª)	PD	-	2	**Thal + CFM + Pred** x 11 (4ª)	PR	4	9	
17*	**VDTPACE** x 2 (2ª)	PR	2	-	**Thal + CFM** x 2 (4ª)	PD	-	-	No grade 3-4 toxicity. Dead 5 months after relapse
18*	Thal + CFM + Dx x 13 (4ª)	PR	8	27	**Len + Dx** (2ª)	PR	3	18	Mild GVHD reactivation with Len. Alive 36 months after relapse
	Len + Dx x 3 (5ª)	PD	-	-					
	VDTPACE x 2 (6ª)	PR	2	-					
19*	**Thal + polychemo** (2ª)	PR	2	6	**Len + Dx** (2ª)	SD	-	8	No grade 3-4 toxicity. Dead 12 months after relapse
20*	**Len + Dx** x 6 (2ª)	VGPR	3	-	**Len + LBH + Dx** x 9 (2ª)	VGPR	6	10	Grade 3 astenia. Alive 65 months after relapse
21*	**Bz + Len + Dx** x 2 (2ª)	SD	-	2	**Poma + Dx** x 9 (3ª)	PR	6	12	
	Thal + Elo + Dx x 3 (3ª)	PD	-	4					No grade 3-4 toxicity. Dead 15 months after relapse
	VDLPACE x 3 (4ª)	PR	2	-					
22*	**Bz/Dx** x 6+ ASCT (1ª)	PR	NA	8	**Len + Carfilz + Dx** x 3 (1ª)	SD	NA	4	No grade 3-4 toxicity. Alive 54 months after transplant
	Len + Dx (2ª)	PR	NA	-	**Poma + Dx** x 8 (2ª)	PR	3	8	
23*	Bz/Dx + ASCT (1ª)	CR	4	30	Bz x 1 (1ª)	-	-	-	Poor performance status at transplantation. Dead after 1 month of monotherapy with Bz
	Thal + CFM + Dx (2ª)	PR	4	-					

Bz indicates bortezomib; PD, progressive disease; Len, lenalidomide; Pred, prednisone; Dx, dexamethasone; LBH, panobinostat; SD, stable disease; Thal, thalidomide; Elo, elotuzumab; CFM, cyclophosphamide; Poma, pomalidomide; PAD, bortezomib + adryamicin + dexamethasone; Ben, bendamustine; NA, not available; Mel, melphalan; Carfilz, carfilzomib;

* Patients who received previous ASCT.

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