Biol Blood Marrow Transplant 24 (2018) 1379–1385

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Phase 1/2 Trial of Carfilzomib Plus High-Dose Melphalan Preparative Regimen for Salvage Autologous Hematopoietic Cell Transplantation Followed by Maintenance Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma

Luciano J. Costa [1,†,*], Heather J. Landau [2,†], Saurabh Chhabra [3], Parameswaran Hari [4], Racquel Innis-Shelton [1], Kelly N. Godby [1], Mehdi Hamadani [4], Roni Tamari [2], Kate Anderton [5], Pamela Dixon [6], Sergio A. Giralt [2]

[1] *Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama*
[2] *Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[3] *Department of Medicine, Medical University of South Carolina, Charleston, South Carolina*
[4] *Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Hollings Cancer Center, Charleston, South Carolina*
[6] *University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, Alabama*

Article history:
Received 27 October 2017
Accepted 27 January 2018

Key Words:
Multiple myeloma
Melphalan
Carfilzomib
Peripheral blood stem cell transplantation
Autologous transplantation

A B S T R A C T

We performed a phase 1/2 trial to investigate the safety and activity of the second-generation proteasome inhibitor Carfilzomib (K) on days -3/-2 in combination with melphalan 200 mg/m^2 (MEL200) on day -2 (K-MEL) in patients with relapsed multiple myeloma (MM) undergoing autologous hematopoietic cell transplantation (phases 1 and 2). Patients without progression received 12 cycles of K maintenance at 36 mg/m^2 days 1, 8, and 15 (schedule A) or days 1, 2, 15, and 16 (schedule B), with patients being treated for 2 cycles in each schedule and on the patient-preferred schedule for the remaining cycles (phase 2). The patients had received a median of 3 previous lines of therapy, 56% had undergone previous AHCT, and 51% had received previous K therapy. During phase 1 (n = 15), the maximum tolerated dose of K in combination with MEL200 was not reached, so the maximum tested dose of 27 mg/m^2 (on day -3) and 56 mg/m^2 (on day -2) was used in phase 2. The rate of very good partial response after K-MEL therapy (n = 44) was 59.2%, compared with 13.7% before K-MEL therapy. Among patients starting maintenance therapy (n = 27), 12-month progression-free survival was 66.7% and 12-month overall survival was 88.1%. There was no strong patient preference for either schedule. Two patients discontinued maintenance due to toxicity. K-MEL followed by K maintenance is safe and active salvage therapy in patients with MM.

INTRODUCTION

Autologous hematopoietic cell transplantation (AHCT) is an established modality in the upfront treatment of patients with multiple myeloma (MM), in whom it improves both the depth and duration of response [1-6] and, in some studies, overall survival (OS) as well [2,3,5,6]. In the relapse setting, AHCT is effective salvage therapy for patients who deferred AHCT as part of initial treatment [1-4] and for patients who experience disease relapse after a first AHCT [7,8].

Melphalan at a dose of 200 mg/m^2 (MEL200) is widely accepted as standard preparative regimen for AHCT in MM [9]. Yet the vast majority of patients will experience relapse, indicating the need to improve preparative regimens for AHCT, particularly in the relapsed setting, where responses tend to be incomplete and less durable [7,8,10]. Although maintenance strategies have been optimized for patients undergoing upfront AHCT [1,2,11-13], with lenalidomide the current standard of care, there is little information and guidance for maintenance therapy after salvage transplantation, particularly when most patients have been exposed and many have become refractory to lenalidomide.

Bortezomib, a first-generation proteasome inhibitor (PI), has been safely combined with MEL200 with apparent increased activity [10,14]. Carfilzomib is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like

Financial disclosure: See Acknowledgments on page 1384.
* Correspondence and reprint requests: Luciano J. Costa, MD, PhD, Department of Medicine, University of Alabama at Birmingham, 1802 6th Avenue South, Birmingham, AL, 35294.
E-mail address: ljcosta@uabmc.edu (L.J. Costa).
† These authors contributed equally to this work.

https://doi.org/10.1016/j.bbmt.2018.01.036
1083-8791/

active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid PI bortezomib. In addition, when measured against a broad panel of proteases, including metalloprotease, aspartyl protease, and serine protease, carfilzomib demonstrated less reactivity against nonproteasomal proteases compared with bortezomib [15,16]. Carfilzomib has recently shown greater activity and induced longer progression-free survival (PFS) than bortezomib in patients with relapsed MM and 1 to 3 previous lines of therapy [17].

We designed a phase 1/2 trial to determine the maximal tolerated dose of carfilzomib that could be safely combined with MEL200 as a preparative regimen in patients undergoing AHCT for relapsed or refractory MM, to determine the activity of this regimen and the safety and efficacy of carfilzomib single agent as maintenance strategy post salvage AHCT.

METHODS

Patient Eligibility

Eligible patients were age ≤70 years, had Eastern Cooperative Oncology Group performance status 0 to 2, and had a diagnosis of symptomatic MM previously treated and with at least 1 previous progression or relapse. Patients were required to have measurable disease at the time of most recent disease progression and to have received salvage conventional therapy with at least a minimal response to the most recent line of therapy (defined as a 25% decline in M protein in serum or urine or in the difference between affected and nonaffected free light chain). Before initiation of study treatment, patients were required to have at least 2×10^6 autologous $CD34^+$ cells/kg of body weight available for transplantation. Patients were also required to have adequate hepatic and hematologic function, and an estimated creatinine clearance ≥40 mL/minute. Previous AHCT was allowed, as long as it was performed >12 months from enrollment, but was not required.

Patients were excluded if they had HIV infection or active hepatitis B or C infection, significant peripheral neuropathy, uncontrolled hypertension or diabetes, unstable angina, or myocardial infarction within 4 months of registration, New York Heart Association class 3 or 4 congestive heart failure or history of significant arrhythmias or nonhematologic invasive malignancy within the past 3 years. Patients who were refractory to carfilzomib therapy were excluded.

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for participation. Onyx/Amgen provided financial support and the investigational product (carfilzomib), but was not involved in the conduction of the study, analysis of results, or writing of the manuscript. The study was registered at ClinicalTrials.gov (NCT 01690143).

Study Design and Endpoints

The study was initially designed as a phase 1/2 study to access the safety and activity of carfilzomib in combination with MEL200 (K-MEL) in the treatment of patients with relapsed or refractory MM. The primary endpoint of phase 1 was the maximal tolerated dose of carfilzomib to be combined with MEL200. The primary endpoint of phase 2 was the rate of very good partial response (VGPR) or better after transplantation in patients treated with K-MEL. As the study completed phase 1, it was amended to include 12 cycles of maintenance therapy with carfilzomib during phase 2; a key secondary endpoint of rate of PFS at the completion of maintenance therapy.

All patients underwent complete staging of their disease before enrollment. Treatment consisted of carfilzomib administered as a 30-minute i.v. infusion on days -3 and -2 before AHCT. Melphalan at dose of 200 mg/m^2 was administered on day -2, at 60 to 120 minutes after the end of infusion of carfilzomib. On day 0, patients received a protocol-defined minimum of 2×10^6 autologous $CD34^+$ cells/kg, intended for hematopoietic reconstitution. The phase 1 portion of the study followed a classical 3 + 3 design. Patients in consecutive cohorts received carfilzomib on days -3 and -2 at doses of 20/27 mg/m^2, 27/27 mg/m^2, 27/36 mg/m^2, 27/45 mg/m^2, and 27/56 mg/m^2. All patients received growth factor support starting on day +1 and continuing until engraftment. The remaining of the supportive care was at the investigator's discretion. Patients were monitored continuously for adverse events, which were compiled and classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. For the purpose of intercohort dose escalation, the following adverse events were considered dose-limiting toxicities: delayed engraftment (beyond 30 days after AHCT), grade 4 or 5 toxicity, other than expected grade 4 hematologic toxicity, some specific grade 3 toxicities (neurologic, cardiovascular, and renal) and any carfilzomib toxicity precluding administration of day -2 carfilzomib dose. Disease response assessment was performed 100 ± 7 days after AHCT.

Patients entering phase 2 of the study received K-MEL AHCT (at dose defined in phase 1) and, in the absence of disease progression on post-AHCT response assessment, 12 cycles of maintenance carfilzomib. During each 28-day cycle of maintenance, patients received carfilzomib at dose of 36 mg/m^2 on days 1, 8, and 15 (schedule A) or 36 mg/m^2 days 1, 2, 15, and 16 (schedule B). Each patient received 2 cycles on each schedule (with initial schedule determined by randomization) and the 8 subsequent cycles on a schedule preferred by the patient. Patient preference was assessed using a numeric scale from 1 to 5, where higher numbers indicate stronger preference. During maintenance, adverse events were monitored continuously, and disease status was assessed at the end of each even cycle. Treatment continued for 12 cycles or until disease progression, treatment intolerance, or withdrawal of consent.

Statistics

The study was designed to enroll 6 to 30 subjects in the phase 1 and approximately 28 subjects in the phase 2, allowing description of the primary endpoint (rate of response VGPR or better) with a half-width <.2 for the 95% confidence interval (CI). We described continuous numerical variables by median and interquartile range. Comparisons between proportions were performed using the chi-square test. OS and PFSPFS curves were generated using the Kaplan-Meier method. Data were collected using REDCap [18], and all statistical analyses were performed using SPSS for Windows, Version 22.0 (IBM, Armonk, NY). In all inference analyses, a 2-sided *P* value <.05 was considered to indicate statistical significance.

RESULTS

Patient Characteristics and Treatments

Fifteen patients were enrolled and treated during phase 1 in 5 consecutive cohorts. Patient characteristics are presented in Table 1. None of the 15 patients developed any dose-limiting toxicity; therefore, the maximum tolerated dose of carfilzomib was not reached, and the maximum tested dose of 27/56 mg/m^2 on days -3/-2 was used in phase 2.

Thirty-three patients consented to participate in the phase 2 of the study. One patient withdrew consent before initiation

Table 1
Characteristics of Patients

Characteristic	Phase 1 (n = 15)	Phase 2 (n = 30)	Total (n = 45)
Age, yr, median (range)	54 (45-68)	60 (41-69)	58 (41-69)
Male sex, n (%)	9 (60)	11 (37)	20 (44)
Race/ethnicity, n (%)			
Non-Hispanic white	7 (47)	19 (63)	26 (58)
Non-Hispanic black	8 (53)	10 (33)	18 (40)
Other	0 (0)	1 (3)	1 (2)
Chromosome abnormalities, n (%)			
t(4;14), t(14;16) or 17p-	2 (13)	4 (13)	6 (13)
Other	9 (60)	23 (77)	32 (71)
None/not available	4 (27)	3 (10)	7 (16)
Previous lines of therapy, median (range)	3 (2-6)	3 (2-5)	3 (2-6)
Previous therapy, n (%)			
AHCT	7 (47)	18 (60)	25(56)
Bortezomib	15 (100)	29 (97)	44 (98)
Carfilzomib	3 (20)	20 (67)	23 (51)
Lenalidomide	12 (80)	29 (97)	41 (91)
Pomalidomide	1 (7)	6 (20)	7 (16)
Salvage therapy before to K-MEL, n (%)			
Bortezomib-based	12 (80)	3 (10)	15 (33)
Carfilzomib-based	3 (20)	20 (67)	23 (51)
Lenalidomide-based	5 (33)	14 (47)	19 (42)
Pomalidomide-based	1 (7)	5 (17)	6 (13)
VGPR or better response before K-MEL, n (%)	2 (13)	4 (13)	6 (13)
$CD34^+$ cells/kg (in 10^6)	4.6 (2.1-9.3)	4.1 (2.2-9.6)	4.1 (2.1-9.6)

of therapy, and 2 patients were subsequently found to be ineligible (1 for being refractory to carfilzomib, 1 for having disease progression at time of enrollment) and were included in the toxicity analysis but not in the efficacy analysis. Thus, a total of 45 patients (15 in phase 1 and 30 in phase 2) were evaluable for the efficacy of K-MEL conditioning therapy (Table 1). Of the 30 patients receiving K-MEL conditioning in phase 2, 1 withdrew consent before completing post-transplantation disease assessment, and 2 had progression of disease at post-transplantation assessment, resulting in 27 patients who started maintenance therapy.

K-MEL Conditioning Therapy

All patients who received K-MEL conditioning and underwent AHCT achieved neutrophil and platelet engraftment after a median of 10 days (range, 8 to 16 days) and 15 days (range, 9 to 24 days), respectively. There were no deaths in the first 100 days post-AHCT. Grade 3-4 nonhematologic toxicities (Table 2) resemble the profile of toxicities seen with MEL200 conditioning.

Table 2
Grades 3 and 4 Nonhematologic Toxicity from K-MEL

Toxicity	Grade 3-4 Nonhematologic, n (%)
Infection	17 (38)
Gastrointestinal	5 (11)
Hypertension	4 (9)
Hypophosphatemia	4 (9)
Rash	3 (7)
Hypokalemia	3 (7)
Syncope	2 (4)
Hypocalcemia	2 (4)
Dyspnea	1 (2)
Atrial fibrillation	1 (2)
Cytokine release syndrome	1 (2)
Hyperglycemia	1 (2)

Among the 44 patients with post-transplantation disease reassessment, 59.1% (95% CI, 44.1% to 72.3%) achieved VGPR or better (Figure 1A), and 61.3% (95% CI, 46.6% to 74.3%) had an improvement in disease response category (eg, from partial response to VGPR). There was no difference in rate of VGPR or better between patients with and without previous AHCT (64.0% versus 52.6%) or between patients with and without previous carfilzomib exposure (59.1% versus 59.1%).

Maintenance Therapy

Of the 29 patients in the phase 2 portion of the study who underwent post-transplantation disease reassessment with intent to pursue maintenance therapy, 2 had disease progression and did not start maintenance. Among the 27 patients who started maintenance therapy, 14 completed the 12 planned cycles, 8 discontinued therapy due to progression, and 2 discontinued therapy due to toxicity. Three patients withdrew consent after 2, 6, and 6 cycles in the absence of progression or adverse event. Among the 29 patients assessed for maintenance therapy, 31.0% showed an improvement in disease response category and 75.8% achieved VGPR or better (Figure 1B). For the 27 patients who received any maintenance, these rates were 33.3% and 81.5% respectively. There were no deaths of patients on therapy. Three patients died during the first 12 months after starting maintenance therapy and after discontinuing therapy due to disease progression. The 12-month PFS and OS for patients starting maintenance therapy were 66.7% (95% CI, 47.7% to 85.7%) and 88.1% (95% CI, 75.3% to 100%), respectively (Figure 2).

The most common adverse events during maintenance were infection (26%), nausea and vomiting (22%) and fatigue (19%) (Table 3). The most common grade 3-4 adverse events were infection (15%), acute kidney injury (11%), and neutropenia (11%). Two patients discontinued maintenance therapy due to an adverse event. One patient with preexisting hypertension discontinued treatment after 8 cycles due to CHF with decline in ejection fraction. One patient developed nausea, vomiting, dehydration with acute kidney injury during

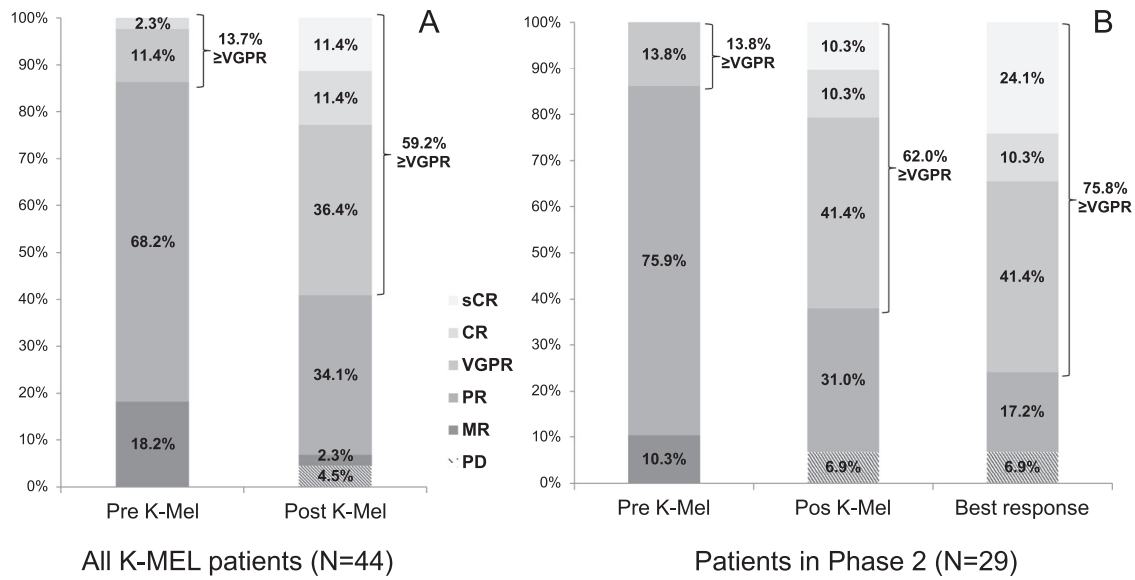

Figure 1. (A) Disease response assessment at completion of pretransplantation salvage therapy and at 100 days post-transplantation with a K-MEL preparative regimen for patients in phases 1 and 2 of the study. (B) Disease response assessment at completion of pretransplantation salvage therapy and at 100 days post-transplantation with K-MEL and best response achieved for patients in phase 2 of the study.

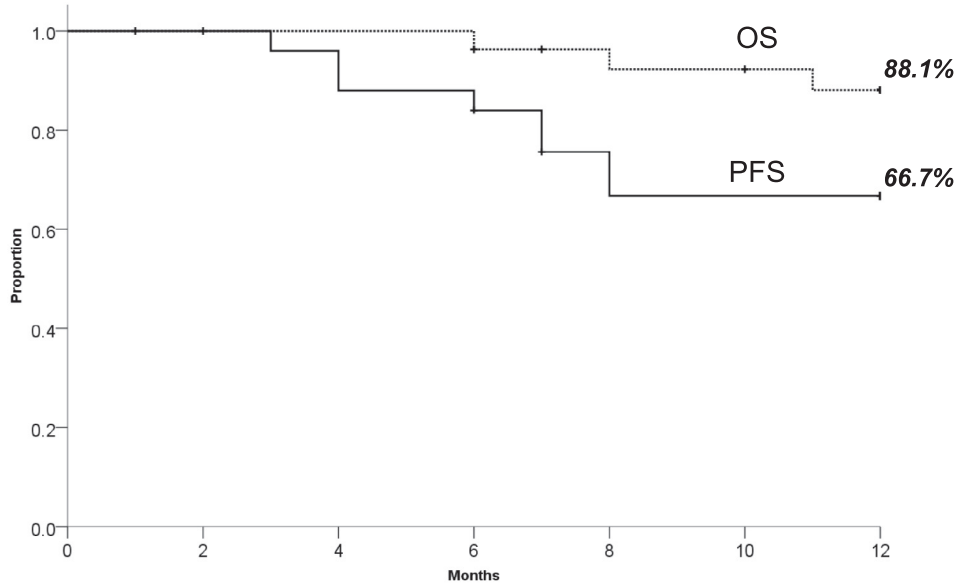

Figure 2. PFS and OS of the patients who entered maintenance therapy.

Table 3
Toxicities During Carfilzomib Maintenance

Toxicity	Any Grade, n (%)	Grade 3-4, n (%)
Infection	7 (26)	4 (15)
Nausea/vomiting	6 (22)	-
Fatigue	5 (19)	1 (4)
Acute kidney injury	4 (15)	3 (11)
Edema	4 (15)	-
Dyspnea	3 (11)	-
Peripheral neuropathy	3 (11)	-
Headache	3 (11)	-
Neutropenia	3 (11)	3 (11)
Diarrhea	3 (11)	1 (4)
Atrial fibrillation	2 (7)	1 (4)
Heart failure/decreased ejection fraction	2 (7)	1 (4)
Hypertension	2 (7)	2 (7)
Confusion	2 (7)	1 (4)
Hypercalcemia	2 (7)	1 (4)
Dehydration	1 (4)	1 (4)
Cholecystitis	1 (4)	1 (4)

first cycle of maintenance carfilzomib. Subsequent renal biopsy was suggestive of thrombotic microangiopathy. There were no deaths on trial or within 30 days of discontinuing trial therapy.

Twenty-four patients completed at least 4 cycles of maintenance therapy and, per the study design, indicated a preference for schedule A or B. Most patients did not have a strong preference for a specific schedule. Twelve patients choose to complete therapy on schedule A, and 12 chose schedule B (Figure 3).

DISCUSSION

By making the administration of high-dose chemotherapy feasible, AHCT provides deeper and longer remissions and improves survival in patients with MM. However, the vast majority of patients with MM treated with AHCT will experience disease progression, indicating an opportunity for improvement in the conditioning regimen. Single-agent melphalan is used as conditioning regimen in >95% of AHCTs for MM performed in the United States [9]. Previous attempts to improve its efficacy by combining it with total body irradiation [19] or with other alkylating agents [20] were met by excessive toxicity.

PI therapy has become a cornerstone of modern MM treatment. Several regimens have combined bortezomib or carfilzomib with conventional doses of alkylating agents with favorable safety profiles and enhanced activity. Among other mechanisms, PIs may prevent nuclear factor-κB-dependent up-regulation of the FA/BRCA DNA repair pathway and magnify the cytotoxic effect of alkylators [21]. This was the rationale to combine bortezomib with high doses of melphalan as AHCT conditioning therapy, an approach that has been taken by several groups [10,14,22-24]. The Intergroupe Francophone du Myelome combined 4 doses of bortezomib with MEL200 in the upfront setting and observed no excessive toxicity and possible greater efficacy than MEL200 (complete response rate of 35% versus 11%) [14]. Lonial et al. [22] also found that bortezomib could be safely combined with MEL200 with 51% of patients achieving VGPR or better in a cohort of patients with suboptimal response to induction therapy. Pharmacodynamics studies indicated greater plasma cell apoptosis when bortezomib was administered after, as opposed to before, MEL200

To our knowledge, this is the first study to explore the combination of carfilzomib and MEL200 before AHCT. Currently, most patients receiving AHCT as part of upfront therapy do so after achieving a VGPR or complete response following induction therapy. Therefore, to obtain meaningful activity data, we opted to perform this study in a population with relapsed or refractory MM (yet responding to salvage therapy), including patients who had undergone previous AHCT. At the doses and schedule tested, we found that carfilzomib can be safely combined with MEL200 with no unexpected toxicity being observed. The regimen was also very active, with 59.1% of patients achieving VGPR or better. However, it is appreciated that the true benefit of the combination of K-MEL is difficult to contextualize due to the heterogeneity of the

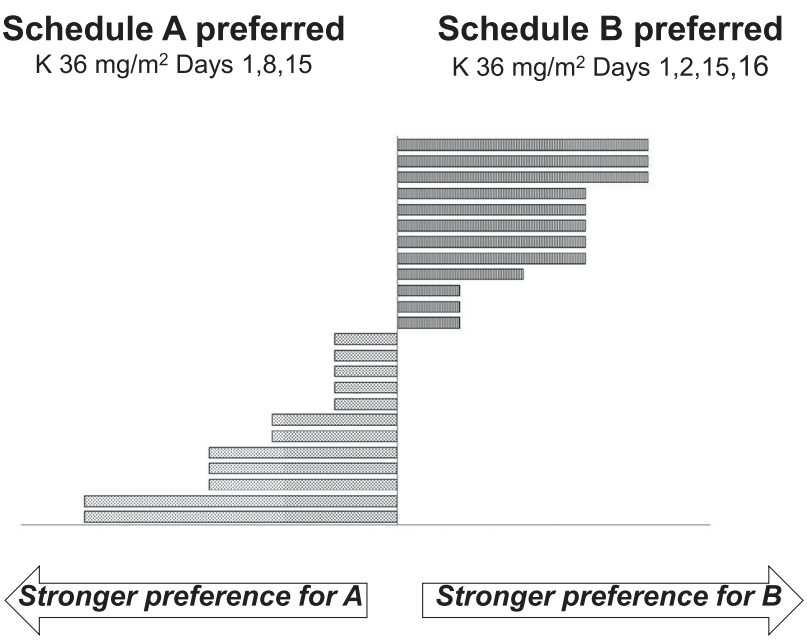

Figure 3. Treatment schedule preference for the patients on maintenance therapy who completed at least 4 cycles.

population and the scarcity of studies with comparable population. One important recent study addressed the value of AHCT with MEL200 conditioning in patients with relapsed MM who had undergone previous AHCT with ≥18 months of remission [7]. In that study, the rate of VGPR or better was 59.5%. Although this is similar to the present study, the population was less heavily pretreated (ie, no previous lenalidomide, pomalidomide, or carfilzomib), was selected based on long remission after AHCT, and had a higher proportion of VGPR or better before AHCT than in K-MEL (38.3% versus 13.7%). Biran et al. [10] recently reported the outcomes of 32 patients with relapsed myeloma undergoing salvage AHCT with MEL200 in combination with bortezomib and found a lower rate of VGPR or better than we report here (34.3% versus 59.1%).

Although we find the efficacy of K-MEL promising, we acknowledge that any comparison with other trial or series needs to be interpreted with caution [7,10,36,37] (Supplementary Table S1), and a prospective, randomized study is needed to demonstrate whether K-MEL is superior to MEL200.

Maintenance therapy has an established role in patients undergoing upfront AHCT with impacts on PFS and OS. Lenalidomide is currently the standard agent in this setting, but data also have been reported supporting maintenance with thalidomide [25-29] or bortezomib [13]. Although salvage AHCT is commonly practiced and supported by high-quality evidence [7,8], there is no standard approach for post-AHCT maintenance therapy in this setting, despite the expectation of greater residual disease burden and shorter remission than after upfront AHCT. The present study demonstrates that single-agent carfilzomib is an active and reasonably well-tolerated maintenance agent in the relapsed setting. Treatment discontinuation due to toxicity was uncommon, and most patients completed the 12 planned cycles of maintenance without severe adverse events or progression.

One potential disadvantage of carfilzomib as a maintenance agent is the requirement for i.v. administration. This can be potentially ameliorated with a less intense schedule than the standard 6 doses per cycle. The Champion-1 study [30] pursued extended therapy with carfilzomib with weekly dosing (3 doses per cycle), reaching a maximum tolerated dose of 70 mg/m^2. Other studies in the newly diagnosed and relapsed setting explored the schedule of 4 doses per cycle (days 1, 2, 15, and 16), at a dose of up to 36 mg/m^2, typically after a period of treatment on a conventional schedule [31,32]. Although a definitive comparison between doses and schedules of carfilzomib for maintenance would require a much larger study, we used this opportunity to access patient preference between 2 schedules with 3 and 4 doses per cycle. Both schedules had reasonable toxicity, with no differences in the pattern of toxicity between the 2 schedules and no clear patient preference. Oprozomib, an orally available carfilzomib analog currently in clinical development, may become a more convenient option for maintenance therapy [33].

In summary, the present study demonstrates that carfilzomib can be safely combined with MEL200 as preparative regimen for AHCT and be used as single agent for post-transplantation maintenance with a reasonable side effect profile. Although the high proportion of patients achieving VGPR or better after K-MEL is encouraging, confirmatory studies directly comparing K-MEL to MEL200 either for upfront AHCT or as a salvage strategy are needed. In the current scenario where more effective upfront and salvage therapies are available and many patients undergo AHCT already in complete remission, such comparisons should be anchored in technologies such as next-generation flow cytometry or next-generation sequencing, allowing detection and quantification of disease burden as low as 10^{-5} to 10^{-6} [34]. The use of carfilzomib post-AHCT should be explored further, particularly in the salvage setting [35]. The doses and schedules explored in the present study can be the backbone for combinations with new agents (eg, monoclonal antibodies, venetoclax), particularly in high-risk patients.

ACKNOWLEDGMENTS

Financial disclosure: This study was supported by MUSC-CTSA, National Institutes of Health National Center for Advancing Translational Sciences (Grant UL1 TR001450), and received financial support and drug support from Onyx-Amgen.

Conflict of interest statement: L.J.C. has received research support from Onyx-Amgen and honoraria from Amgen. P.H. has received honoraria from Celgene, Sanofi, and Takeda. S.A.G. has received honoraria from Sanofi, Celgene, Takeda and Amgen. There are no conflicts of interest to report.

Authorship statement: L.J.C.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, writing (original draft). H.J.L.: conceptualization, investigation, methodology, and writing (review and editing); S.C.: data curation, investigation, methodology, and writing (review and editing); P.H.: data curation, formal analysis, investigation, and writing (review and editing); R.I.-S.: investigation and writing (review and editing); K.N.G.: investigation and writing (review and editing); M.H.: investigation and writing (review and editing); R.T.: investigation and writing (review and editing); K.A.: data curation, formal analysis, project administration, resources, and writing (review and editing); P.D.: data curation, formal analysis, project administration, resources, and writing (review and editing); S.A.G.: conceptualization, formal analysis, funding acquisition, investigation, methodology, and writing (review and editing).

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.01.036.

REFERENCES

1. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376:1311-1320.
2. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371:895-905.
3. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16:1617-1629.
4. Cavo M, Beksac M, Dimopoulos MA, et al. Intensification therapy with bortezomib-melphalan-prednisone versus autologous stem cell transplantation for newly diagnosed multiple myeloma: an intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial). *Blood*. 2016;128:673.
5. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348:1875-1883.
6. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med*. 1996;335:91-97.
7. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2016;3:e340-e351.
8. Michaelis LC, Saad A, Zhong X, et al. Salvage second hematopoietic cell transplantation in myeloma. *Biol Blood Marrow Transplant*. 2013;19:760-766.
9. Costa LJ, Zhang MJ, Zhong X, et al. Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:1615-1624.
10. Biran N, Rowley SD, Vesole DH, et al. A phase I/II study of escalating doses of bortezomib in conjunction with high-dose melphalan as a conditioning regimen for salvage autologous peripheral blood stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22:2165-2171.
11. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1782-1791.
12. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.
13. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol*. 2012;30:2946-2955.
14. Roussel M, Moreau P, Huynh A, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myelome (IFM). *Blood*. 2010;115:32-37.
15. Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. *Cancer Res*. 2007;67:6383-6391.
16. Arastu-Kapur S, Anderl JL, Karus M, et al. *Clin Cancer Res*. 2011;17:2734-2743. PMID is 21364033.
17. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17:27-38.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
19. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*. 2002;99:731-735.
20. Lahuerta JJ, Mateos MV, Martínez-López J, et al. Busulfan 12 mg/kg plus melphalan 140 mg/m^2 versus melphalan 200 mg/m^2 as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study. *Haematologica*. 2010;95:1913-1920.
21. Yarde DN, Oliveira V, Mathews L, et al. Targeting the Fanconi anemia/BRCA pathway circumvents drug resistance in multiple myeloma. *Cancer Res*. 2009;69:9367-9375.
22. Lonial S, Kaufman J, Tighiouart M, et al. A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedule-finding study. *Clin Cancer Res*. 2010;16:5079-5086.
23. Rodriguez TE, Hari P, Stiff PJ, Smith SE, Sterrenberg D, Vesole DH. Busulfan, melphalan, and bortezomib versus high-dose melphalan as a conditioning regimen for autologous hematopoietic stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22:1391-1396.
24. Nishihori T, Alekshun TJ, Shain K, et al. Bortezomib salvage followed by a phase I/II study of bortezomib plus high-dose melphalan and tandem autologous transplantation for patients with primary resistant myeloma. *Br J Haematol*. 2012;157:553-563.
25. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinical Trials Group Myeloma 10 Trial. *Blood*. 2013;121:1517-1523.
26. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.
27. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354:1021-1030.
28. Lokhorst HM, van der Holt B, Zweegman S, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood*. 2010;115:1113-1120.
29. Maiolino A, Hungria VT, Garnica M, et al. Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma. *Am J Hematol*. 2012;87:948-952.
30. Berenson JR, Cartmell A, Bessudo A, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. *Blood*. 2016;127:3360-3368.
31. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372:142-152.
32. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. 2012;120:1801-1809.

33. Ghobrial IM, Savona MR, Vij R, et al. Final results from a multicenter, open-label, dose-escalation phase 1b/2 study of single-agent oprozomib in patients with hematologic malignancies. *Blood*. 2016;128:2110.
34. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17:e328-e346.
35. Hari P, Mateos MV, Abonour R, et al. Efficacy and safety of carfilzomib regimens in multiple myeloma patients relapsing after autologous stem cell transplant: ASPIRE and ENDEAVOR outcomes. *Leukemia*. 2017;31:2630-2641.
36. Nieto Y, Valdez BC, Pingali SR, et al. High-dose gemcitabine, busulfan, and melphalan for autologous stem-cell transplant in patients with relapsed or refractory myeloma: a phase 2 trial and matched-pair comparison with melphalan. *Lancet Haematol*. 2017;4:e283-e292.
37. Gimsing P, Hjertner Ø, Abildgaard N, et al. Salvage bortezomib-dexamethasone and high-dose melphalan (HDM) and autologous stem cell support (ASCT) in myeloma patients at first relapse after HDM with ASCT. A phase-2 trial. *Bone Marrow Transplant*. 2015;50:1306-1311.