Phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma

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ABSTRACT

The purpose of this study was to assess the safety and efficacy of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma. Patients with multiple myeloma who had relapsed after at least one prior treatment were eligible to participate. In the dose escalation part of the study a standard 3+3 design was used to determine the maximum tolerated dose of four planned dose levels of the combination of carfilzomib and panobinostat. Panobinostat was administered on days 1, 3, 5, 15, 17, and 19. Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. Treatment was continued until progression or intolerable toxicity. Forty-four patients were accrued into the trial, 13 in the phase I part and 31 in the phase II part of the study. The median age of the patients was 66 years and the median number of prior therapies was five. The expansion dose was established as 30 mg panobinostat, 20/45 mg/m^2 carfilzomib. The overall response rate was 67% for all patients, 67% for patients refractory to prior proteasome inhibitor treatment and 75% for patients refractory to prior immune modulating drug treatment. At a median follow up of 17 months, median progression-free survival was 7.7 months, median time to progression was 7.7 months, and median overall survival had not been reached. The regimen was well tolerated, although there were several panobinostat dose reductions. In conclusion, the combination of panobinostat and carfilzomib is feasible and effective in patients with relapsed/refractory multiple myeloma. *(Trial registered at ClinicalTrials.gov: NCT01496118)*

Introduction

Multiple myeloma (MM) is a disease characterized by the accumulation of plasma cells in the bone marrow which can result in bone marrow failure, bone destruction, hypercalcemia, and renal failure.[1] It is predicted that in 2014, approximately 24,000 cases of MM will be diagnosed and 11,090 people will die of the disease (~2% of all cancer deaths) in the United States alone[2] and MM makes up approximately 13% of hematologic cancers worldwide.[1] Despite an increasing number of therapeutic options and improved survival over the last two decades, MM is generally thought to be incurable. Most patients receive multiple lines of therapy during the course of their disease; however, responses remain transient and the duration of response shortens with each relapse.[3] New therapies and drug combinations are needed to address this problem.

Proteasome inhibitors have dramatically changed the treatment landscape for MM. Bortezomib, with its proven activity and well-defined toxicity, was the first proteasome inhibitor approved by the Food and Drug Administration (FDA).[4] Since then, newer generation proteasome inhibitors have been developed. Carfilzomib is an irreversible inhibitor of the chymotrypsin-like active sites of the 20S proteasome.[5,6] Unlike its predecessor, carfilzomib produces a minimal amount of peripheral neuropathy.[7] In 2012, carfilzomib was approved as a single agent for the treatment of MM in patients who had received at least two prior therapies. This approval was based on a phase II study that showed an overall response rate (ORR) of 23.7%, and manageable toxicities in relapsed and refractory MM patients treated with the drug.[8,9]

Panobinostat is a pan-inhibitor of class I, II and IV histone deacetylases which increases acetylation of proteins involved in multiple oncogenic pathways, including the aggressome protein degradation pathway.[10] Preclinical studies have shown synergistic cytotoxicity in MM cell lines with the combination of a proteasome inhibitor and panobinostat.[11,12] Combination treatment with panobinostat and bortezomib has been shown to be tolerable and efficacious in relapsed/refractory MM patients.[10,13] Early data on panobinostat revealed that the route of administration (intravenous or oral) and the schedule (continuous or intermittent) play an important roles in the toxicity profile of the drug.[10,14-17]

Based on encouraging pre-clinical and clinical data demonstrating activity of proteasome inhibitors and panobinostat, we conducted a phase I/II study of carfilzomib plus panobinostat in patients with relapsed/refractory MM.

Methods

Study design and objectives

This study was a single-arm, open-label, multicenter phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory MM. The primary objective of the phase I part was to determine the maximum tolerated dose (the highest dose at which one or none of six patients experienced dose-limiting toxicity

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during the first treatment cycle) or maximum planned dose (the highest dose planned in the dose escalation part) if the maximum tolerated dose was not reached. The primary objective of the phase II part was to assess the efficacy of the combination; the primary endpoint was ORR. Secondary endpoints were time to progression, progression-free survival and overall survival, calculated using Kaplan-Meier methods.

The study was registered with ClinicalTrials.gov (NCT01496118) and conducted according to the ethical principles of the Declaration of Helsinki, in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice. The protocol was approved by the Institutional Review Boards of participating sites and patients were enrolled following written informed consent.

Patients

Eligible patients had to have progressed during or after one or more previous treatment regimens and had to have measurable disease defined by International Myeloma Working Group (IMWG) guidelines. Patients had to meet standard organ function criteria, including cardiac function (see *Online Supplement*), and were excluded if they had received previous histone deacetylase treatment.

Treatment schedule

In the phase I part of the study, a 3+3 design was used to determine the maximum tolerated dose of the combination. Four dose levels were evaluated (Table 1). Patients continued treatment until disease progression or intolerable toxicity. The definition of dose-limiting toxicity is given in the *Online Supplement.*

Safety and efficacy assessments

Patients who received one or more doses of the protocol treatment were followed for toxicity. All adverse events and serious adverse events were graded according to the National Cancer Institute's Common Terminology for Adverse Events (CTCAE) version 4.0.[18] Responses were classified based on the IMWG Uniform Response Criteria[19] except for minimum response, which was defined according to the European Group for Blood and Marrow Transplant.[20]

Statistical analysis

For the efficacy analysis, the treated population was defined as all patients who received one or more dose of both carfilzomib and panobinostat and underwent one or more response assessment. Sample size was based on the historic ORR of 18% for single-agent carfilzomib treatment of relapsed/refractory MM.[21] A sample size of 27 (plus 10% for potential non-evaluable patients) provided an 80% power to detect an increase in the ORR to 36% (a 100% increase) based on a one-sided test of proportion at an alpha level of 0.10.

Time to progression was defined as the interval of time between first administration of study treatment and the earlier of the date of tumor progression or the date of last adequate tumor assessment. Progression-free survival was defined as the interval of time between first administration of study treatment and the earlier of the date of disease progression or the date of death due to any cause. Overall survival was defined as the interval from first study treatment until the earlier of the date of death or date last known to be alive.

Results

Patients' characteristics

Between January 2012 and April 2013, 44 patients with relapsed/refractory MM were accrued into the study (13 patients in the phase I part and 31 patients in the phase II part). A summary of the patients' baseline characteristics is given in Table 2. The median age of the patients was 66 years (range, 41-82). Sixty-one percent of the patients were female. The majority of patients (78%) were in International Staging System stages 1 and 2 at diagnosis. Twenty-five percent of patients had adverse prognostic cytogenetics or fluorescence *in situ* hybridization at the time of enrollment, including 11% with 17p deletion. The median number of prior therapies was five (range, 1-10) including prior bortezomib in 89% of cases, prior immune modulating drugs in 89% of cases and prior stem cell transplantation in 52% (Table 2). Thirty-six percent of patients were refractory (defined as having progressive disease while on, or within 60 days, of treatment) to proteasome inhibitors, 30% were refractory to immune modulating drugs, 14% were refractory to both bortezomib and immune modulating drugs, and 43% were refractory to their last treatment regimen (Table 2).

Patients' disposition and treatment administered

Of the 44 patients enrolled in the study, nine (21%) remained on study treatment as of June 2014 and 35 had discontinued treatment. Eighteen (41%) patients discontinued due to disease progression. Nine (20%) patients discontinued due to either the patients' decision or the physicians' discretion (including one patient who discontinued treatment in order to undergo autologous hematopoietic stem cell transplantation). Four patients (9%) discontinued treatment due to treatment-related adverse events (anemia, decreased left ventricular ejection fraction, supraventricular tachycardia, and heart failure), and four patients (9%) discontinued due to non-related adverse events (stroke, pneumonia, and confusion/memory loss). Two patients died on study, one due to progres-

Table 1. Dose escalation study.

Dose Level	Panobinostat	Carfilzomib	Patients
1	20 mg PO TIW days 1, 3, 5, 15, 17, and 19	20 mg/m^2 cycle 1, days 1 and 2 27 mg/m^2 for all subsequent doses (20/27 mg/m^2)	4*
2	20 mg PO TIW days 1, 3, 5, 15, 17, and 19	20 mg/m^2 cycle 1, days 1 and 2 36 mg/m^2 for all subsequent doses (20/36 mg/m^2)	3
3	20 mg PO TIW days 1, 3, 5, 15, 17, and 19	20 mg/m^2 cycle 1, days 1 and 2 45 mg/m^2 for all subsequent doses (20/45 mg/m^2)	3
4	30 mg PO TIW days 1, 3, 5, 15, 17, and 19	20 mg/m^2 cycle 1, days 1 and 2 45 mg/m^2 for all subsequent doses (20/45 mg/m^2)	3

**One patient discontinued due to rapid disease progression and was replaced. PO:* per OS; *TIW: thrice weekly.*

sive disease and one due to heart failure, and are included in the breakdown of reasons for discontinuation. The median number of cycles of treatment completed was six (range, 1-27), with 12 patients (27%) having completed >12 cycles.

Phase I patients

Patients were treated on four dose levels as outlined in Table 1. No dose-limiting toxicities were observed at any of the planned dose levels so the expansion dose was established as the maximum planned dose/dose level 4 (See Table 1).

Phase II patients

Thirty-one patients were enrolled in the phase II expansion part of the study at the maximum planned dose. Combining the three patients treated at dose level 4 in the phase I trial and the 31 patients from the expansion cohort, there were 34 patients treated at dose level 4 (30 mg panobinostat and 20/45 mg/m^2 carfilzomib).

Efficacy

Response to treatment is shown in Table 3. When patients in the phase I and phase II parts of the study were included, 42 patients were evaluable for response (2 patients came off study prior to their first response assessment). The ORR of all evaluable patients was 67% and the clinical benefit rate was 79%. Thirty-three percent had a very good partial response or better, 33% had a partial response, 12% a minimum response, 17% stable disease, and 5% had disease progression. The ORR for all patients treated at the maximum planned dose (dose level 4) was 72% and the clinical benefit rate was 88% with 38% having a very good partial response or better, 34% having a partial response, 16% having a minimum response, 6% having stable disease and 6% having disease progression. The patients' response improved with increased treatment cycles. The ORR after 4, 8, and 12 cycles were 62%, 68%, and 75%, respectively.

Prior treatments did not appear to affect response rates. The ORR for all evaluable patients who had previously been treated with bortezomib was 70%. Patients who were refractory to bortezomib, immune modulating drugs, or both had an ORR of 67%, 75%, and 80%, respectively (Table 3). Although the numbers are small, high risk, as defined by traditional cytogenetics and/or fluorescent *in situ* hybridization did not appear to affect response (Table 3).

With a median follow up of 17 months (range, 3.5-29.8) for all evaluable patients, the median Kaplan-Meier progression-free survival was 7.7 months (95% CI: 4.4-16.8 months) (Figure 1A) and the median time to progression was 7.7 months (95% CI: 4.8-not yet reached) (Figure 1B). The overall survival rate of all patients at 24 months was 67% (0.48, 0.79) and the median has not been reached. As expected, patients who were refractory to prior immune modulating drugs or bortezomib had shorter progression-free survival, time to progression and overall survival than the whole population of patients (Figure 1A-C). Depth of response correlated with better outcome, as evidenced by the duration of response curves in Figure 2. Patients whose best response was a partial response had a median duration of response of 11.6 months (range, 3.9-14.9) while the median duration of response has not been reached for patients with a very good partial response or better.

Safety

Table 4 provides a summary of all grade 3/grade 4 treatment-related toxicities.

Grade 3/4 treatment-related adverse events included thrombocytopenia (17 patients, 38%), neutropenia (9 patients, 21%), fatigue (5 patients, 11%), anemia (4 patients, 9%) and hypertension (4 patients, 9%). Salient, all-grade common toxicities often associated with proteasome inhibitors and panobinostat are summarized in Table 5. Diarrhea, nausea and vomiting, and thrombocytopenia were the most commonly seen toxicities. Except

Table 2. Characteristics of the patients (n=44).

Age, median (range), years	66 (41-82)
Gender, n. (%)	
Female	27 (61%)
Male	17 (39%)
Race, n. (%)	
Caucasian	34 (77%)
African American	8 (18%)
Other/unknown	1 (2%)
Unknown	1 (2%)
ECOG, score n. (%)	
0	19 (43%)
1	20 (46%)
2	4 (9%)
Unknown	1 (2%)
ISS stage, n. (%)	
1	20 (46%)
2	14 (32%)
3	5 (11%)
Unknown	5 (11%)
Fluorescence *in situ* hybridization, n. (%)	
Normal	17 (39%)
Abnormal	15 (34%)
1q amp*	6 (14%)
1p del*	0
t(4;14)*	5 (11%)
t(11;14)	7 (16%)
t(14;16)*	6 (14%)
17p deletion*	5 (11%)
Unknown/not done	12 (27%)
Cytogenetics, n. (%)	
Normal	35 (80%)
13q*	0
Hyperdiploid	4 (9%)
Unknown	5 (11%)
All poor risk patients*, n. (%)	11 (25%)
Median number of prior therapies (range)	5 (1-10)
Prior therapies, n. (%)	
IMiD	39 (89%)
Proteasome inhibitors	39 (89%)
Either IMiD or proteasome inhibitors	43 (97%)
Both IMiD and proteasome inhibitors	35 (80%)
Stem cell transplantation	23 (52%)
Refractory to prior therapies, n. (%)	
Both IMiD and proteasome inhibitors	6 (14%)
Either IMiD or proteasome inhibitors	23 (52%)
Proteasome inhibitors	16 (36%)
IMiD	13 (30%)
Last therapy	19 (43%)

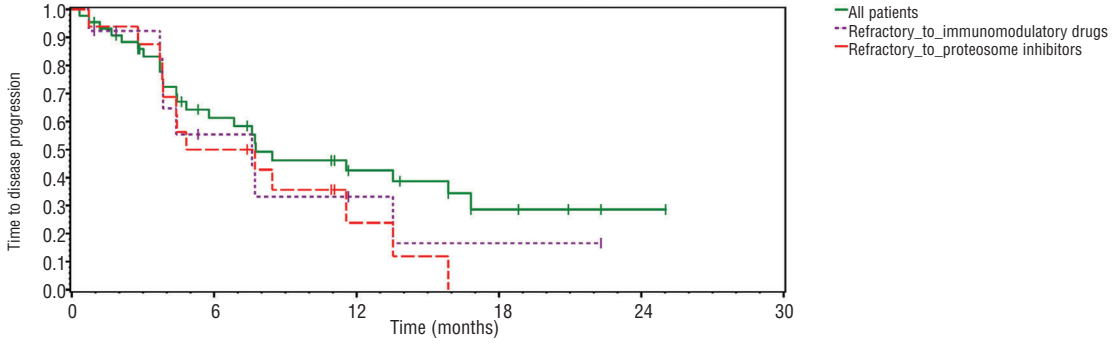
**Poor-risk patients: FISH showing 1q amp, or 1p del, or t(4;14), or t(14;16), or 17p del, or cytogenetics 13 q del; IMiD: immune modulating drug.*

Table 3. Response to treatment.

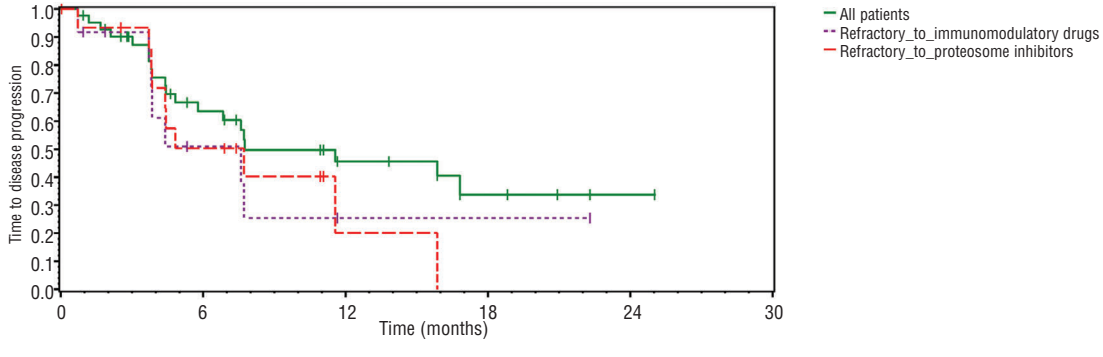
Response assessment	All patients n=42	Dose level 4 n=32	Prior bortezomib n=37	Refractory to bortezomib n=15	Refractory to IMiD n=12	Dual refractory n=5	High risk* n=11	Standard risk** n=21
ORR, n. (%)	28 (67%)	23 (72%)	26 (70%)	10 (67%)	9 (75%)	4 (80%)	8 (73%)	15 (71%)
CBR, n. (%)	33 (79%)	28 (88%)	31 (84%)	13 (87%)	11 (92%)	5 (100%)	9 (82%)	16 (76%)
≥VGPR, n. (%)	14 (33%)	12 (38%)	13 (35%)	3 (20%)	5 (42%)	1 (20%)	5 (46%)	8 (38%)
PR, n. (%)	14 (33%)	11 (34%)	13 (35%)	7 (47%)	4 (33%)	3 (60%)	3 (27%)	7 (33%)
MR, n. (%)	5 (12%)	5 (16%)	5 (14%)	3 (20%)	2 (17%)	1 (20%)	1 (9%)	1 (5%)
SD, n. (%)	7 (17%)	2 (6%)	5 (14%)	2 (13%)	1 (8%)	0	1 (9%)	4 (19%)
P D, n. (%)	2 (5%)	2 (6%)	1 (3%)	0	0	0	1 (9%)	1 (5%)

**High risk is defined as fluorescence* in situ *hybridization showing (FISH) 1q amp, or 1p del, or t(4;14), or t(14;16), or 17p del, or cytogenetics 13 q del. **Excludes patients without FISH data.IMiD: immune modulating drug.*

A Kaplan-Meier progression-free survival curves.



B Kaplan-Meier time to progression curves.



C Kaplan-Meier overall survival curves.

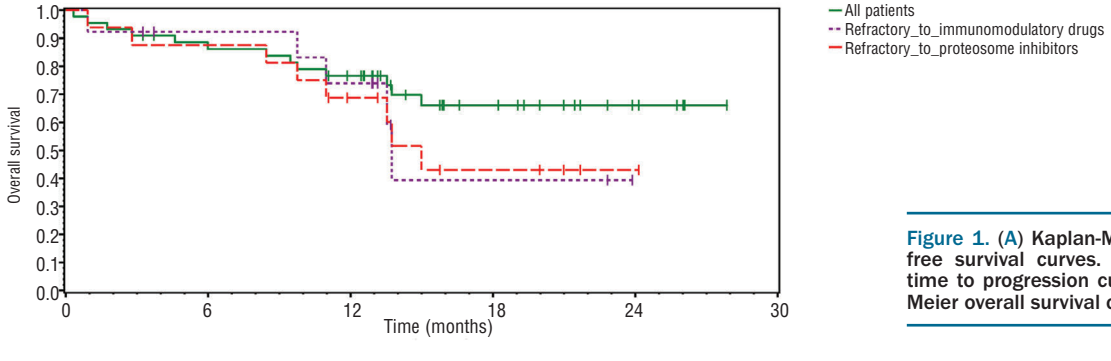


Figure 1. (A) Kaplan-Meier progression-free survival curves. (B) Kaplan-Meier time to progression curves. (C) Kaplan-Meier overall survival curves.

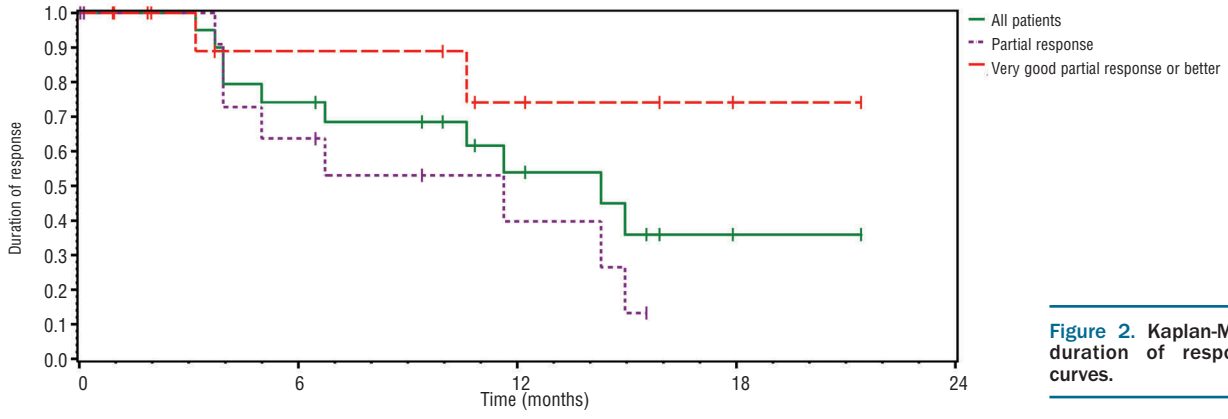


Figure 2. Kaplan-Meier duration of response curves.

for thrombocytopenia, nearly all toxicities were grade 1 or 2. Neuropathy, as expected, was not frequently reported and was mostly grade 1. There were 14 treatment-related serious adverse events affecting 12 patients (27%) and there was one treatment-related death due to heart failure. One patient died of the underlying disease while on study. Three patients (7%) discontinued treatment due to treatment-related toxicity (anemia, decreased left ventricular ejection fraction, and supraventricular tachycardia). The three patients with cardiac-related serious adverse events were all elderly (73, 74 and 80 years of age) with risk factors for coronary artery disease including diabetes mellitus, hypercholesterolemia, tobacco use, and hypertension. The doses of panobinostat ranged from 15 mg to 30 mg and the doses of carfilzomib ranged from 20 mg/m^2 to 45 mg/m^2. The onset of the serious adverse events was disparate with one patient having symptoms within the first week of therapy, one after three cycles of therapy and one after six cycles.

Dose

In patients treated at the maximum planned dose/expansion dose level (30 mg panobinostat and 20/45 mg/m^2 carfilzomib), dose reductions for panobinostat were seen in 59% of the patients and there were three panobinostat-only discontinuations (Figure 3). The toxicity associated with panobinostat often resolved during the weeks off therapy so cumulative toxicity was not apparent. Unfortunately, the toxicities were recurrent with subsequent exposure. Thus, although there were no dose-limiting toxicities or dose reductions during the time frame for evaluation dose-limiting toxicity, there were several dose reductions of panobinostat in patients treated at the expansion dose. The average panobinostat dose delivered was 23.6 mg (79% of the planned dose). Carfilzomib dose reductions were seen in only 18% of the patients at the expansion dose level and there were no carfilzomib-only discontinuations. The average carfilzomib dose delivered was 41.6 mg/m^2 (92% of the planned dose).

Discussion

The combination of carfilzomib and oral panobinostat was well tolerated and the maximum tolerated dose was

Table 4. Incidence of all grade 3/4 treatment-related toxicities*, and treatment related deaths (n=44).

	Grade 3	Grade 4	Total
Hematologic, n. (%)			
Thrombocytopenia	16 (36%)	1 (2%)	17 (38%)
Neutropenia	8 (18%)	1 (2%)	9 (21%)
Anemia	4 (9%)	0	4 (9%)
Leukopenia	3 (7%)	0	3 (7%)
Non-hematologic, n. (%)			
Fatigue	5 (11%)	0	5 (11%)
Hypertension	4 (9%)	0	4 (9%)
Diarrhea	3 (7%)	0	3 (7%)
Dyspnea	3 (7%)	0	3 (7%)
Nausea	2 (5%)	0	2 (5%)
Pneumonia	2 (5%)	0	2 (5%)
Vomiting	2 (5%)	0	2 (5%)
Atypical hemolytic-uremic syndrome	0	1 (2%)	1 (2%)
Abdominal pain	1 (2%)	0	1 (2%)
Alanine aminotransferase increased	1 (2%)	0	1 (2%)
Alkaline phosphatase increased	1 (2%)	0	1 (2%)
Aspartate aminotransferase increased	1 (2%)	0	1 (2%)
Asthenia	1 (2%)	0	1 (2%)
Chest pain	1 (2%)	0	1 (2%)
Confusion	1 (2%)	0	1 (2%)
Heart failure	1 (2%)	0	1 (2%)
Hypercalcemia	1 (2%)	0	1 (2%)
Hyponatremia	1 (2%)	0	1 (2%)
Proteinuria	1 (2%)	0	1 (2%)
Treatment-related death**	1 (2%)		

*Per CTCAE V 4.0. **Heart Failure.

Table 5. Common toxicities expected with panobinostat and carfilzomib.

	All patients (n=44)			
	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	21 (48%)	9 (20%)	3 (7%)	0
Nausea and vomiting	19 (43%)	10 (23%)	2 (5%)	0
Thrombocytopenia	8 (18%)	8 (18%)	16 (36%)	1 (2%)
Neuropathy	3 (7%)	2 (5%)	0	0
Dyspnea	7 (16%)	4 (9%)	2 (5%)	0

not reached among the planned dose levels. The ORR and clinical benefit rate were 67% and 79%, respectively, in a heavily pretreated population who had received a median of five prior therapies. Although prior exposure to bortezomib was not a prerequisite for enrollment, nearly all patients enrolled (89%) had been treated with bortezomib. Furthermore, over half the patients (52%) were refractory to a proteasome inhibitor or immune modulatory drug and 43% of patients were refractory to their last therapy prior to enrolling on trial. Interestingly, the ORR did not differ for the different subsets of populations including those with prior bortezomib exposure and/or refractoriness. The ORR in this study compares favorably with the ORR of 23.7% and 34.5% reported with single-agent carfilzomib[8,9] and the PANORAMA 2 study of bortezomib with panobinostat,[13] respectively. Recently, the results of the PANORAMA 1 study of bortezomib/dexamethasone/panobinostat were reported: the ORR was 60.7%.[22] Our results continue to compare favorably despite a much more heavily pre-treated population and without the incorporation of dexamethasone. Similarly, responses thus far appear durable, with a median progression-free survival and time to progression of 7.7 months and nearly one-third of patients receiving more than 12 cycles of therapy. Additionally, the overall survival has not been reached with a median follow-up of 17 months.

Although there were no dose-limiting toxicities in the dose escalation part of the study and the maximum tolerated dose was not reached, there were several dose reductions in patients treated in the expansion dose part (Figure 3). The toxicity profile for carfilzomib has been well established at the currently FDA-approved dose of 20 mg/27 mg[8,9] and is still being defined, but thus far is not significantly different, for doses up to 20 mg/56 mg.[23-25] Toxicities attributed to panobinostat in this trial are similar to those reported in other studies with this drug.[13,16,26,27] In particular there are two ongoing studies of carfilzomib/panobinostat combinations looking at alternative schedules of panobinostat compared to that used in this study. Preliminary results have been reported.[16,27]

Interestingly the route and schedule of administration of panobinostat seem to be important for the degree and type of toxicities seen.[10,14-17]

The oral route with intermittent dosing seems to be the most tolerable and allows a longer duration of treatment.[10] In the PANORAMA studies panobinostat was given orally at a dose of 20 mg thrice weekly for 2 consecutive weeks with 1 week off; cycles were repeated every 21 days to accommodate bortezomib dosing.[13,22] The most notable toxicities observed were thrombocytopenia and diarrhea with significant improvements to baseline after the 1 week break.[13,22] In the current study, panobinostat was given in a thrice weekly schedule every other week of a 28-day cycle. The schedule fits well with the

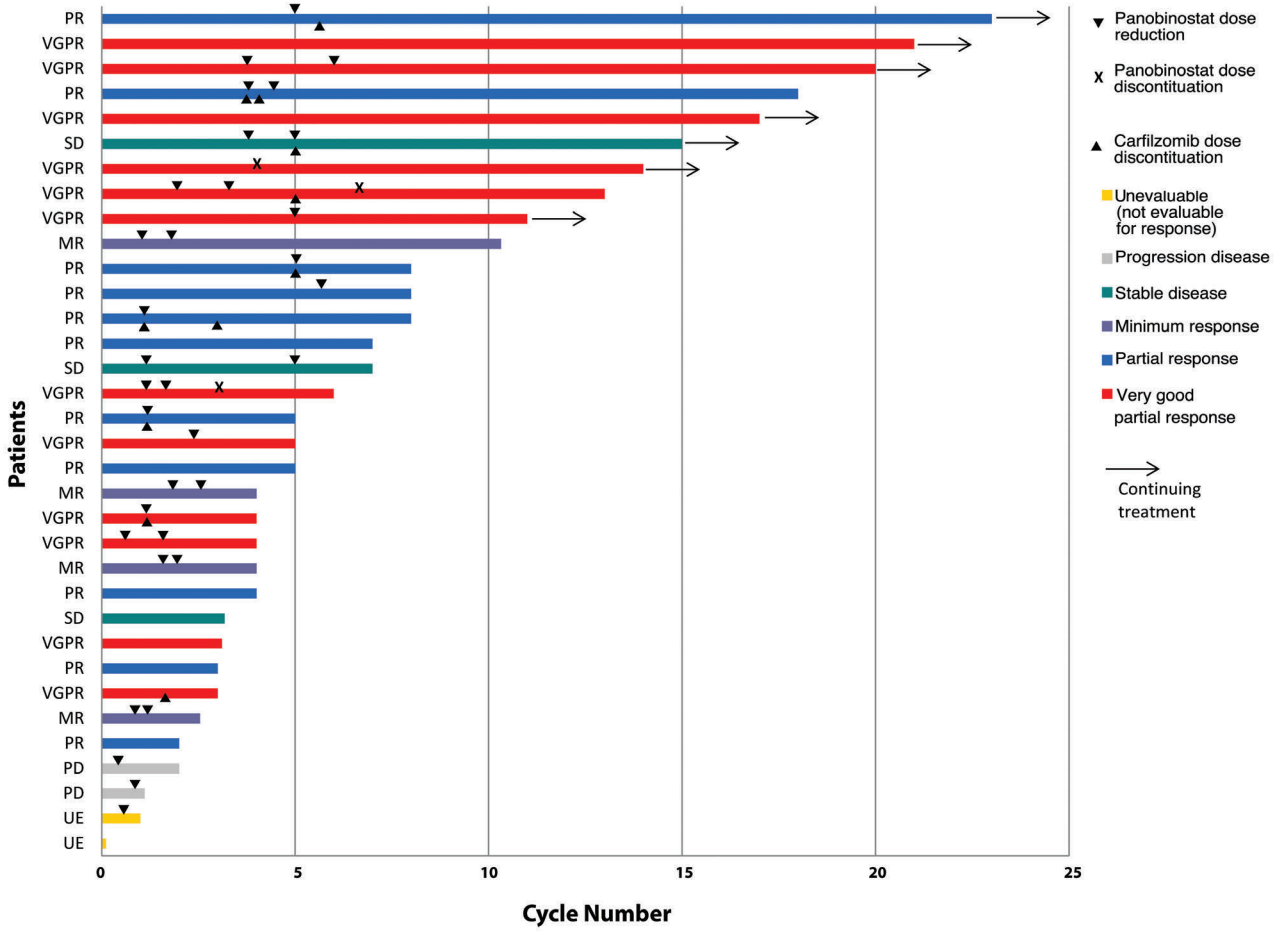


Figure 3. Dose reductions and discontinuations of expansion/maximum planned dose.

traditional 28-day cycle of carfilzomib and also capitalizes on the intermittent dosing to help mitigate toxicity. Despite 20 mg being the maximum dose used in the bortezomib combinations,[10] we were able to escalate the dose of panobinostat to 30 mg without dose-limiting toxicities. However, 59% of patients originally treated at the expansion dose ultimately required panobinostat dose reductions due to emerging toxicities. As a result the average dose delivered to all patients was 23.6 mg. The dose of carfilzomib was relatively well tolerated with only 18% of patients requiring dose reductions. Given emerging data that carfilzomib doses above 20/45 mg/m^2 are safe and feasible,[28] and the possibility that carfilzomib dosing may be optimized by capping the dose of panobinostat at 20 mg thrice weekly,[16] we decided to test further dose levels of the combination with plans for a parallel dose expansion at that dose level if tolerated. These studies are underway.

In summary, the combination of carfilzomib and panobinostat is safe, tolerable and highly efficacious in patients with relapsed and/or refractory MM. Further evaluation of this combination is warranted and will help to establish the optimal dose and schedule.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046-1060.
2. National Cancer Institute. (homepage on the internet.) Cited 2014. Available from: http://seer.cancer.gov/statfacts/html/mulmy.html.
3. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004;79(7):867-874.
4. Cavo M. Proteasome inhibitor bortezomib for the treatment of multiple myeloma. Leukemia. 2006;20(8):1341-1352.
5. Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007;67(13):6383-6391.
6. Arastu-Kapur S, Shenk K, Parlati F, Bennett M. Non-proteasomal targets of proteasome inhibitors bortezomib and carfilzomib. Blood (ASH Annual Meeting Abstracts), 2008;112(11):2657.
7. Arastu-Kapur S, Anderl JL, Kraus M, et al. Nonproteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: a link to clinical adverse events. Clin Cancer Res. 2011;17(9):2734-2743.
8. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120(14):2817-2825.
9. Vij R, Siegel DS, Jagannath S, et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol. 2012;158(6):739-748.
10. San-Miguel JF, Richardson PGG, Sezer O, et al. A phase Ib study of oral panobinostat and IV bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol. 2011;29(15 Suppl):8075.
11. Atadja P. Development of the pan-DAC inhibitor panobinostat (LBH589): successes and challenges. Cancer Lett. 2009;280(2):233-241.
12. Catley L, Weisberg E, Kiziltepe T, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood. 2006;108(10):3441-3449.
13. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood. 2013;122(14):2331-2337.
14. Sharma S, Beck J, Mita M, et al. A phase I dose-escalation study of intravenous panobinostat in patients with lymphoma and solid tumors. Invest New Drugs. 2013;31(4):974-985.
15. Zangari M, Berno T, Talamo G, et al. Phase I exploratory study of iv formulation of panobinostat in combination with bortezomib in relapsed/refractory multiple myeloma patients: effect on serum PTH and gene expression profiling (GEP) studies. Blood (ASH Annual Meeting Abstracts). 2012;120(21):4073.
16. Shah JJ, Thomas SK, Weber DM, et al. Phase 1/1b study of the efficacy and safety of the combination of panobinostat + carfilzomib in patients with relapsed and/or refractory multiple myeloma. Blood (ASH Annual Meeting Abstracts). 2012;120(21):4081.
17. Berdeja JG, Hart L, Lamar R, et al. Phase I/II study of panobinostat and carfilzomib in patients (pts) with relapsed or refractory multiple myeloma (MM), interim phase I safety analysis. Blood (ASH Annual Meeting Abstracts). 2012;120(21):4048.
18. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. US Department of Health and Human Services. 2010.
19. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.
20. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high dose therapy and haemopoietic stem cell transplantation: Myeloma Subcommittee of the EBMT, European Group for Blood and Marrow Transplant. Br J Haematol. 1998;102(5):1115-1123.
21. Jagannath S, Vij R, Stewart K, et al. The Multiple Myeloma Research Consortium (MMRC). Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM). J Clin Oncol. 2009;27(15 Suppl):8504.
22. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomized, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-1206.
23. Papadopoulos KP, Siegel DS, Vesole DH, et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. J Clin Oncol. 2015;33(7):732-739. .
24. Badros AZ, Papadopoulos KP, Zojwalla N, et al. A phase 1b study of 30-minute infusion carfilzomib 20/45 and 20/56 mg/m2 plus 40 mg weekly dexamathasone in patients in patients with relapsed and/or refractory (R/R) multiple myeloma. Blood (ASH Annual Meeting Abstracts). 2012;120(21):4036.
25. Lendvai N, Landau H, Lesokhin A, et al. Phase II study of infusional carfilzomib in patients with relapsed or refractory multiple myeloma. Blood (ASH Annual Meeting Abstracts). 2012;120(21):947.
26. Wolf JL, Siegel D, Goldschmidt H, et al. Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. Leuk Lymphoma. 2012;53(9):1820-1823.
27. Kaufman JL, Zimmerman T, Rosenbaum CA, et al. Phase I study of the combination of carfilzomib and panobinostat for patients with relapsed and refractory myeloma: a Multiple Myeloma Research Consortium (MMRC) clinical trial. Blood (ASH Annual Meeting Abstracts). 2014;124(21):32.
28. Lendvai N, Hilden P, Devlin S, et al. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood. 2014;124(6):899-906.