Recapturing disease response: A phase 2 study of carfilzomib 56 mg/m² in patients with relapsed or refractory multiple myeloma who have progressed on carfilzomib 27 mg/m²

To the Editor:

Despite the improvement in overall survival (OS) for patients with multiple myeloma (MM) over the last decade due to the approvals of novel agents, most patients with MM suffer multiple relapses and eventually develop refractory disease, resulting in a continued need for novel treatment strategies for relapsed and refractory MM (RRMM).

Carfilzomib, a selective proteasome inhibitor, was initially approved for the treatment of RRMM as monotherapy at a dose of 20/27 mg/m² (CFZ 20/27) twice weekly. Subsequently, carfilzomib has been approved in combination with lenalidomide and dexamethasone at a dose of 20/27 mg/m² twice weekly. And, in combination with dexamethasone at a dose of 20/56 mg/m² twice weekly, or 20/70 mg/m² once weekly based on the phase 3 clinical trials ASPIRE, ENDEAVOR, and A.R.R.O.W.

In a post hoc analysis of phase 2 trials of single-agent carfilzomib examining the dose-outcome relationships in MM patients receiving a starting dose of carfilzomib 20 mg/m² escalated to a target dose of 27 mg/m², logistic regression modeling suggested a dose-response relationship with carfilzomib. However, there are no published studies evaluating the efficacy of dose escalation after progression on CFZ 20/27. We conducted a single-center, phase 2, open-label study designed to evaluate the efficacy of CFZ 20/56 monotherapy in RRMM patients who had previously received and were refractory to CFZ 20/27 including in combination with other anti-myeloma agents (NCT01775553). Herein we present our results.

The protocol was approved by the institutional review board, and all patients provided informed consent. Adult patients with symptomatic MM with ≥2 prior lines of therapy including both a proteasome inhibitor and an immunomodulatory agent, who had progressed on and were refractory to CFZ 20/27 without any...
carfilzomib related grade 3-4 adverse events (AEs) were eligible. Prior CFZ 20/27 regimens could have included combinations of other agents that were FDA approved, off-label, or as part of an investigational clinical trial.

Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of 28 day cycles. During cycle 1, patients received doses of 20 mg/m² if it had been greater than 4 weeks since their last carfilzomib dose or 56 mg/m² if they had received carfilzomib within the previous 4 weeks. All subsequent doses were 56 mg/m² if the initial doses were tolerated. Prior to carfilzomib administration, all patients received 8 mg dexamethasone as a premedication.

The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety, best overall response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), and OS. Responses were assessed according to the International Myeloma Working Group Uniform Response Criteria. AEs were assessed according to the Common Terminology Criteria for AEs v4.0. As patients were required to have progressive disease and be refractory to CFZ 20/27 at study entry, the null hypothesis was that the median PFS would be approximately 2 months. Therefore, the study treatment would be considered successful if the lower limit of a two-sided 95% confidence interval of median PFS estimated on a Kaplan-Meier curve was greater than 2 months. With a sample size of 37, there would be 90% power to detect an improvement in median PFS from 2 to 3.5 months with a two-sided alpha of 5%.

Thirteen patients were enrolled. Twelve patients completed at least one cycle and were evaluable for efficacy. The median age was 65 (range: 55-76) and patients had received a median of six prior lines of therapy. Baseline characteristics are summarized in Table S1. The median time between patients becoming refractory to a CFZ 20/27 containing regimen and the present study was 3.12 (0.7-13.63) months. Patients completed a median of four (1-16) cycles of treatment on study. In all but one patient the reason for treatment discontinuation was progression of disease. One patient came off study per investigator discretion due to grade 4 elevated gamma-glutamyl transpeptidase that was possibly related to carfilzomib. After enrollment of 13 patients, the study was closed as accrual became challenging due to widespread use of CFZ doses greater than 20/27.

With CFZ 20/56 and only premedication dosing of dexamethasone, of the 12 patients evaluable for efficacy, the ORR was 33%, CBR was 50%, and median PFS was 3.2 months. These results compare favorably with the outcomes patients had previously attained when they were CFZ naïve and treated with CFZ 20/27 that is, ORR, CBR, and PFS of 33%, 42%, and 3.7 months, respectively (Table S2). For patients responding (i.e., partial response [PR]) to CFZ 20/56, the median DOR was 5.6 (1-10) months. The PFS and response when subjects had been carfilzomib naïve and were treated with 20/27 containing regimens was compared to the PFS and response on CFZ 20/56 in a swimmers plot (Figure 1). A comparison of PFS and response when patients had been on CFZ 20/27 vs CFZ 20/56 is illustrated in Figure S1.

All AEs considered to be related to CFZ 20/56 are listed in Table S3. The most common AEs of any grade were thrombocytopenia (54%), anemia (38%), acute kidney injury (38%), hypertension (38%), headache (31%), neutropenia (23%), and dyspnea (23%).

In this phase 2 study, CFZ 20/56 was well tolerated with grade 3 hypertension seen only in two patients (15%) and no patients developed clinically evident congestive heart failure, echocardiographic evidence of reduced ejection fraction, or significant elevations in brain natriuretic peptide levels. Moreover, in this heavily pre-treated patient population, CFZ 20/56 monotherapy was active in patients refractory to prior CFZ 20/27 therapy, with an ORR of 33%, CBR of 50%, and PFS of 3.2 months. Additionally, a significant number of patients had a period of disease stabilization on CFZ 20/56 such that the Kaplan-Meier curve for PFS on prior CFZ 20/27 therapy overlapped with PFS for CFZ 20/56 on current study.

Results from the relevant randomized phase 2 SWOG S1304 study comparing CFZ 20/56 vs 20/27 in patients with RRMM were recently presented. Although patients who received CFZ 20/56 vs 20/27 had higher VGPR rates, there was no significant difference in PFS or OS. Crossover between low-dose and high-dose carfilzomib was allowed and a total of 16 patients crossed over due to disease progression. In contrast to our study which found that CFZ 20/56 was able to recapture responses in CFZ 20/27-refractory patients, no responses (MR or better) were noted among the 16 patients who crossed over from the CFZ 20/27 to 20/56 group. The difference in response seen to CFZ 20/56 in patients refractory to CFZ 20/27 in our study compared to the SWOG S1304 study is unclear, although time to dose-escalation could be considered a contributing factor. In the SWOG S1304 study, all patients were increased to CFZ 20/56 while progressing on CFZ 20/27 compared to our study in which most patients were refractory to carfilzomib in a previous line of therapy not immediately preceding study enrollment. However, time to dose-escalation does not likely fully account for the difference as 4 of 12 evaluable patients in our study were refractory to a carfilzomib-containing regimen immediately prior to study entry, two of which achieved SD and two of which achieved MR on CFZ 20/56.

The major limitation of the current study is the changing landscape of carfilzomib therapy for RRMM. There are now varying carfilzomib regimens approved based on phase 3 trial data as discussed previously, and numerous early phase trials of carfilzomib utilizing differing dosing schemas and combination agents. Given the heterogeneity in patient populations, dosing/schedule, and partner agents of carfilzomib across studies, it is difficult to make cross study comparisons and the optimal carfilzomib-based regimen remains unclear. The choice of carfilzomib therapy should be carefully balanced based on patient and disease characteristics as well as known AEs of the regimens. Although there is growing use of carfilzomib at initial doses higher than 20/27 mg/m² based on the current approvals of carfilzomib and evolving clinical trial data, the results of this study remain relevant. In particular, for patient populations that may be started on CFZ 20/27, such as older patients or those with medical comorbidities that may put them at greater risk for toxicities, the approach in this study not only optimizes safety by ensuring tolerance of CFZ 20/27 before dose escalation, but also may decrease costs. In
conclusion, our findings suggest that patients who tolerate CFZ 20/27 containing regimens but eventually progress on them may benefit from subsequent dose escalation to CFZ 20/56.

ACKNOWLEDGMENT

We thank the patients and their families for their willingness to participate in clinical trials. This work was funded and supported by Onyx Pharmaceuticals, which was acquired by Amgen in August 2013.

CONFLICT OF INTEREST

HJC has given sponsored lectures for DAVA Oncology. SP is a consultant for Foundation Medicine, Inc. DM has given sponsored lectures for Shire and is a consultant for Foundation Medicine, Inc. DC and DV have given sponsored lectures for Celgene. SJ is on the Scientific advisory boards for Celgene, Bristol-Myers Squibb, and Sanofi-Aventis. AC is a consultant for Takeda Pharmaceuticals and Novartis, is on the scientific advisory board for Array BioPharma, Celgene, Takeda Pharmaceuticals, Novartis, and Onyx Pharmaceuticals, and has given sponsored lectures for Celgene. The remaining authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

HJC, SP, BB, DM, LI, TG, AD, GM, DC, DV, EF, SJ, and AC were responsible treating patients and data acquisition. KG, MHY, LL, JG, and EC were responsible for research data management, coordination of the clinical research, and analysis of the data. AC and SJ conceptualized the study and wrote the protocol. AC was the principal investigator. KB, LS, and AC analyzed the data and wrote the manuscript. All authors approved the final manuscript.

Kevin Barley1, Larysa Sanchez1, Hearn J. Cho1, Samir Parekh1, Deepu Madduri1, Joshua Richter1, Luis Isola2, Talia Goldstein3, Amishi Dhadwal1, Katarzyna Zarychta1, Gillian Morgan Sanchez1, Donna Catamero1, Daniel Verina1, Erika Florendo1, Moon-hee Yum4, Lisa La5, Jude Gullie1, Elaine Chan1, Sundar Jagannath1, Ajai Chari1

1Multiple Myeloma Program, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York
2Bone Marrow and Stem Cell Transplant Program, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York

Correspondence
Ajai Chari, Multiple Myeloma Program, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1185, New York, NY 10029.
Email: ajai.chari@mountsinai.org

ORCID
Larysa Sanchez https://orcid.org/0000-0001-9353-7680

REFERENCES


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