TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2018) 48: 80-83

doi:10.3906/sag-1611-97

Carfilzomib experience in relapsed/refractory multiple myeloma: a single-center experience

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Received: 23.11.2016 • **Accepted/Published Online:** 11.01.2018 • **Final Version:** 23.02.2018

Background/aim: Carfilzomib (CFZ) is a new-generation proteasome inhibitor with significant activity in relapsed or refractory multiple myeloma (R/R-MM). We have retrospectively evaluated R/R-MM patients who were treated with CFZ plus dexamethasone.

Materials and methods: Twenty-one R/R-MM patients who were treated with CFZ plus dexamethasone between October 2013 and January 2016 were screened. The patients were followed until March 2016 after CFZ treatment.

Results: Ten (47.6%) of the patients were female and 11 (52.4%) of them were male. The median age was 62 (47–76) years. The median number of prior treatment lines was 3 (2–7). The median number of administered cycles of treatment for CFZ was 4 (1–10). The median overall response rate was 26.3%. The most common hematological adverse events were anemia and thrombocytopenia (38%). The most common nonhematological adverse event was fatigue (71.4%). One patient died because of a cerebrovascular event and 1 patient died because of pneumonia during the treatment period. The median duration of response rate and time to next therapy were 8 (7–9) and 3 (2–16) months, respectively. The median overall survival was 8 (0.5–33) months.

Conclusion: Despite the small number of patients, our results suggest that CFZ provides acceptable responses in heavily pretreated R/R-MM patients.

Key words: Multiple myeloma, carfilzomib, proteasome inhibitors, novel therapies

1. Introduction

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells and accounts for approximately 10% of hematologic malignancies (1,2). In newly diagnosed cases of MM, initial treatment depends on whether the patient is a candidate for autologous stem cell transplant (ASCT) with high-dose melphalan. Younger (<65 years) and fit patients are potential candidates for ASCT with high-dose melphalan. Before the ASCT, VAD (vincristine, doxorubicin, dexamethasone), bortezomib-based, or thalidomide-based regimens are being used as induction therapy (3). Melphalan, bortezomib, or immunomodulatory (thalidomide, lenalidomide)-based regimens are preferred for initial treatment in elderly (>65 years) and unfit patients who are ineligible for ASCT (4).

MM, which has a high response rate to first-line treatments and long durations of remission, has a high risk of relapse, and relapsed/refractory MM (RR-MM) is more resistant than de novo disease to known therapeutic agents. Remissions are shorter and the possibility of toxicity is higher with recurrent disease (5). In recent years, the use of thalidomide and lenalidomide, immunomodulatory drugs (IMiDs), and bortezomib, a proteasome inhibitor, increased the success of survey and remission durations in RR-MM. However, patients with RR-MM may develop resistance and succumb to the disease. Patients who are resistant to both lenalidomide and bortezomib have a poor prognosis and are accepted as cases of double-refractory MM (6,7). The median progression-free survival and overall survival (OS) are respectively 5 and 9 months in patients with double-refractory MM (8).

Carfilzomib (CFZ) is a new promising agent for double-refractory MM. CFZ is a second-generation proteasome inhibitor with significant activity among RR-MM patients. In this study, we evaluated the efficacy and toxicity of CFZ in our patients who received bortezomib and lenalidomide prior to our study and who developed RR-MM.

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2. Materials and methods

2.1. Patients

In this study, 21 RR-MM patients treated with CFZ plus dexamethasone between October 2013 and January 2016 in the Hematology Department of Ege University were retrospectively screened. The patients were followed until March 2016. During the aforementioned period, carfilzomib was not available in our country, so we used the drug with special permission from our health authority for patients who were resistant to bortezomib and lenalidomide.

Patients had received at least 2 lines of prior regimens for relapsed/refractory disease according to the International Myeloma Working Group (IMWG), including bortezomib, thalidomide or lenalidomide, an alkylating agent, or an anthracycline alone or in combination. The International Scoring System (ISS) was used for prognostic evaluation at the beginning of treatment (9).

Side effects (hematological or nonhematological) and treatment dose of carfilzomib, duration of treatment, response assessments, response rates, and survival status of patients were evaluated. Overall response rate (ORR; the proportion of patients with stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR]) was assessed according to the IMWG Uniform Response Criteria (10). Adverse events were assessed at each visit and graded according to National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events (Version 4.0) (11).

2.2. Treatment

Carfilzomib was given by intravenous infusion over 2–10 min on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle; the daily dose for cycle 1 was 20 mg/m^2 and the dose was increased to 27 mg/m^2 per day in cycle 2 and subsequent cycles. Doses were modified at the treating physician's discretion. All patients received dexamethasone at 20–40 mg/week. Intravenous and oral hydration was given prior to CFZ.

2.3. Statistical analysis

Patient characteristics were summarized using descriptive statistics such as median, minimum and maximum were used for qualitative data, and a number with percentage was used for categorical data. OS was determined by Kaplan–Meier analysis. OS was defined as the beginning of CFZ treatment to death from any cause or last contact. Time to next therapy (TtNT) was defined as the time from the first dose of CFZ to the beginning of the next therapy. The duration of response (DOR) was calculated from the time of first recorded achievement of a particular response level, i.e. PR, VGPR, CR, or sCR, and includes only patients responding to the progression of disease or death without disease progression.

3. Results

3.1. Patients and disease characteristics

In this study, 21 RR-MM patients treated with CFZ were evaluated; 10 (47.6%) of them female and 11 (52.4%) of them male. The median age at CFZ initiation was 62 (range: 47–76) years. The median time from diagnosis of MM to the beginning of CFZ was 45 (range: 20–137) months. Before CFZ initiation, all patients were assessed as having relapsed/refractory disease. Patients and disease characteristics are given in Table 1.

3.2. Treatment characteristics

Patients had received a median of 3 lines of therapy prior to CFZ (range: 2–7). CFZ was given as 3rd line therapy for 9 patients, 4th line therapy for 6 patients, 5th line therapy for 5 patients, and 8th line therapy for 1 patient. Refractoriness to bortezomib and IMiDs prior to CFZ treatment was seen in 42.8% and 61.9% of patients, respectively. Thirteen patients (61.9%) were refractory in their last treatments.

Table 1. Patients and treatment characteristics at the beginning of CFZ.

Patients	N: 21 (%)
Male	10 (47.6)
Female	11 (52.4)
Age (median)	62 (range: 47–76)
ECOG	
0–2	15 (71.4)
3–4	6 (28.6)
ISS	
II	6 (28.6)
III	15 (71.4)
M protein	
IgG	11 (52.3)
IgA	6 (28.6)
Light chain	4 (19.1)
Light chain	
Kappa	15 (71.4)
Lambda	6 (28.6)
Extramedullary plasmacytoma (%)	4.7
Prior lines of therapy (median)	3 (2–7)
Bortezomib resistance (%)	42.8
IMiD resistance (%)	61.9

The median time from last treatment to CFZ initiation was 2 months (range: 0.5–21). The median time from diagnosis to CFZ initiation was 45 months (range: 20–137). The most common last therapy before CFZ was lenalidomide-based treatment (61.9%). Fourteen patients (66.6%) had prior ASCT.

3.3. Treatment characteristics with carfilzomib

The median number of administered cycles of treatment for CFZ was 4 (range: 1–10). The majority of patients (90.5%) received CFZ according to the 20/27 mg/m^2 dose schedule. Two patients (9.5%) received CFZ at a maximal dose as 56 mg/m^2. All patients received CFZ therapy as a combination with dexamethasone.

Two patients died before response assessment, and therefore they were not included in the response analysis. The ORR was 26.3%, with 5 patients with PR in this study. Eight (42.1%) patients had disease progression and 6 (31.6%) patients had SD. Their treatment regimens were changed. The median DOR was 8 (range: 7–9) months. The median TtNT and OS were 3 (range: 2–16) and 8 (range: 1–33) months, respectively.

3.4. Adverse events

During the treatment, no infusion-related side effects were observed in any patients. The most common hematological adverse events were thrombocytopenia and anemia (38%). The most common nonhematological adverse event was fatigue (71.4%). At baseline, 40% of patients had neuropathy. Two patients (9.5%) experienced new-onset neuropathy but no patients had worsening neuropathy. CFZ-related adverse events are illustrated in Table 2.

Table 2. Treatment-related adverse events.

	All grades (%)	Grade ≥3 (%)
Hematological		
Thrombocytopenia	8 (38)	3 (14.2)
Neutropenia	6 (28.5)	4 (19)
Anemia	8 (38)	3 (14.2)
Nonhematological		
Fatigue	15 (71.4)	6 (28.5)
Nausea	14 (66.7)	4 (19)
Dyspnea	3 (14.2)	1 (4.8)
Pneumonia	2 (9.5)	1 (4.8)
Peripheral neuropathy	2 (9.5)	0
Acute renal failure	1 (4.8)	0
Cerebrovascular event	1 (4.8)	1 (4.8)

Seven patients died at the end of the study. One patient died because of cerebrovascular event and 1 patient died because of pneumonia during the treatment period. The treatment-related mortality rate was 9.5%. Five patients died because of disease progression after the CFZ treatment was changed.

4. Discussion

Carfilzomib is an irreversible second-generation proteasome inhibitor and received fast approval from the US FDA for RR-MM patients in July 2012. Robust and durable efficacy and acceptable safety and high tolerability profile were proven in patients with clinical trials (12). In this study, we evaluated the efficacy and safety of CFZ plus dexamethasone treatment in heavily pretreated patients who had received prior bortezomib, immunomodulatory agents like thalidomide or lenalidomide, and alkylating agents.

In our group, the ORR was 26.3% and the best response was PR. The median DOR was 8 months. The median number of prior treatment lines was 3 and 13 patients (61.9%) were refractory in their last treatments. Refractoriness to bortezomib and IMiDs prior to CFZ treatment was seen in 42.8% and 61.9% of patients, respectively. Fourteen patients (66.6%) had prior ASCT. The median OS was 8 months. In the pivotal study, PX-171-003A1, 266 patients with RR-MM who had received at least 2 prior treatment regimens were treated with single-agent CFZ. The median number of prior therapies was 5, 74% of patients had been treated with autologous transplantation, and the majority of patients (95%) were judged refractory to their most recent therapy. The ORR was 23.7% with a median DOR of 7.8 months. The median OS rate was 15.6 months (12). In another phase 2 single-agent CFZ study, the best ORR was 17.1% and the median DOR and OS were >10.6 and 29.9 months, respectively. The median number of prior therapies was 3 and 80% of patients had been treated with autologous transplantation (13). In the randomized phase 3 study of CFZ (FOCUS), the median OS was 10.2 vs. 10.0 months with carfilzomib vs. low-dose corticosteroids. There was no significant improvement between groups. The median ORR was 19.1% in the CFZ group and 11.4% with low-dose corticosteroids (14). Although the number of patients was limited, our results were compatible with literature.

In our group, the most common hematological adverse events were thrombocytopenia (38%), anemia (38%), and neutropenia (28.5%). The most common nonhematological adverse events were fatigue (71.4%), nausea (66.7%), and dyspnea (28.5%). Adverse events were manageable. In the literature, hematological adverse events are the prominent toxicity of CFZ treatment. The most common hematological adverse events were found

to be thrombocytopenia (28.3%–39%), anemia (26.8%–56%), and neutropenia (15%–25.7%). The most common nonhematological adverse events were fatigue (49%–62.9%, 77.8%), nausea (20%–60%), and dyspnea (34%–37.1%) (12–15). All these side effects were temporary and easy to manage, but bleeding due to thrombocytopenia or neutropenic fever may cause severe clinical conditions (16). Our findings are compatible with the literature. In a study from Israel, both hematological (76.3% for anemia, 75.6% for thrombocytopenia) and nonhematological (77.8% for fatigue) adverse events were reported to be higher than in previous studies. It was reported that the higher number of adverse events were associated with the combination of drugs (17). The treatment-related mortality rate was 9.5% in our group. This mortality rate was higher than those seen in the literature (4.1%–5.2%) (12,17). It should be kept in mind that our study group had a small number of patients and the cerebrovascular event that was one of the causes of death was only suspiciously related to carfilzomib.

Our study had some limitations. First, it was a retrospective study with a potential bias concerning patients and methods. Second, the number of patients was limited since it was a single-institution experience.

Despite the small number of patients, our results suggest that carfilzomib provides acceptable responses in heavily pretreated RR-MM patients. Carfilzomib seems to be tolerable and the side effects were manageable.

References

1. Kariyawasan CC, Hughes DA, Jayatillake MM, Mehta AB. Multiple myeloma: causes and consequences of delay in diagnosis. QJM-Int J Med 2007; 100: 635-640.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics 2014. CA Cancer J Clin 2014; 64: 9-29.
3. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, Sezer O, Ludwig H, Dimopoulos MA, Attal M et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood 2011; 117: 6063-6073.
4. Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Blade J, Mateos MV, Rosinol L, Boccadoro M, Cavo M, Lokhorst H et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). Blood 2011; 118: 4519-4529.
5. Kumar SK, Therneau TM, Gertz MA, Lacy MQ, Dispenzieri A, Rajkumar SV, Fonseca R, Witzig TE, Lust JA, Larson DR et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc 2004; 79: 867-874.
6. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352: 2487-2498.
7. Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, Haessler J, Feather J, Hoering A, Moreau P et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia 2012; 26: 149-157.
8. Kumar K, Blade J, Crowley J, Goldschmidt H, Hoering A, Jagannath S, Klein S, Lahuerta J, Laubach J, Lee J et al. Outcome of patients with myeloma relapsing after IMiD and bortezomib therapy: a multicenter study from the International Myeloma Foundation Working Group. Haematologica 2010; 95: 151.
9. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, Boccadoro M, Child JA, Avet-Loiseau H, Kyle RA et al. International staging system for multiple myeloma. J Clin Oncol 2005; 23: 3412-3420.
10. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467-1473.
11. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, Cella D. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 2003; 13: 741-748.
12. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, Trudel S, Kukreti V, Bahlis N, Alsina 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: 2817-2825.
13. Vij R, Siegel DS, Jagannath S, Jakubowiak AJ, Stewart AK, McDonagh K, Bahlis N, Belch A, Kunkel LA, Wear 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: 739-748.
14. Hájek R, Masszi T, Petrucci MT, Palumbo A, Rosiñol L, Nagler A, Yong KL, Oriol A, Minarik J, Pour L et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia 2017; 31: 107-114.
15. Nooka AK, Badros AZ, Patel P, McCulloch L, Lonial S, Kaufman JL. Hematologic safety data from four phase II studies of single-agent carfilzomib in relapsed and/or refractory multiple myeloma. ASCO Meeting Abstracts 2012; 30: 8086.
16. Harvey RD. Incidence and management of adverse events in patients with relapsed and/or refractory multiple myeloma receiving single-agent carfilzomib. Clin Pharmacol 2014; 6: 87-89.
17. Muchtar E, Gatt ME, Rouvio O, Ganzel C, Chubar E, Suriu C, Tadmor T, Shevetz O, Lavi N, Shochat T et al. Efficacy and safety of salvage therapy using Carfilzomib for relapsed or refractory multiple myeloma patients: a multicenter retrospective observational study. Br J Haematol 2016; 172: 89-96.