

Low-Dose Carfilzomib Plus Dexamethasone Regimen in a Cardiac Patient with Multiple Myeloma who had Multiple Comorbidities: A Case Report

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Abstract

Patients with multiple myeloma are often treated with chemotherapy or a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) plus lenalidomide plus dexamethasone. Data for the appropriate treatment of patients with multiple comorbidities is limited. Dose modification has been explored in older patients with multiple myeloma, who often have decreased cardiac, pulmonary, renal, hepatic, or neurologic function and may have trouble tolerating treatment. We present the case of a 59-year-old Egyptian woman with multiple comorbidities who was diagnosed with stage II multiple myeloma and was not eligible for transplant. All available chemotherapy drugs were contraindicated due to multiple comorbidities. She was initially treated with radiotherapy and bortezomib plus lenalidomide plus dexamethasone but experienced an intestinal obstruction on treatment. After laparotomy and jejunal resection, treatment was restarted (lenalidomide was omitted) but the patient experienced significant peripheral neuropathy and treatment was changed to a low dose modified regimen of carfilzomib plus dexamethasone. The patient has completed seven treatment cycles. Treatment has been well tolerated and has demonstrated clinical effectiveness. Physicians treating patients who are unable to tolerate conventional treatment regimens should consider modified regimens and closely monitor patients for adverse events which may require dose modification or a change in treatment.

Keywords: Carfilzomib; Dexamethasone; Multiple Myeloma

Background

Multiple myeloma, which accounts for 10% of all hematological malignancies [1] had a global incidence of 176,404 and mortality of 117,077 in 2020, with a 5-year prevalence of 450,579 [2]. Agents such as lenalidomide and bortezomib have improved overall survival times for patients with multiple myeloma [3-6]. However, some particularly vulnerable patients, such as those with comorbidities or older patients, may experience adverse events or reduced tolerability when treated using commonly utilized regimens. Patients with comorbidities are underrepresented in oncology clinical trials [7].

Data regarding treatment of patients with significant comorbidities is limited; however, older patients (> 65) with multiple myeloma may benefit from lower dose intensity treatment regimens, particularly if they have reduced cardiac, pulmonary, renal, hepatic, or neurologic function [8]. Individualized treatment with tailored dosing may be effective at improving tolerability and optimizing efficacy. This

approach to treatment may also prove beneficial to younger patients with significant comorbidities. We report a case in which a modified treatment regimen using low-dose carfilzomib plus dexamethasone was safe and well tolerated in a patient with multiple myeloma for whom all available chemotherapy regimens were contraindicated due to comorbidities. This modified treatment regimen demonstrated clinical effectiveness in our patient.

Case Presentation

Our patient was a 59-year-old Egyptian woman who presented with fatigue, dizziness, and headache which she had been experiencing for several weeks (October 2019). There was no fever, lymphadenopathy, hepatosplenomegaly, rash, or history of peripheral neuropathy. Her vital signs were stable and she had a normal level of consciousness (Glasgow Coma Scale: 15). The patient had mild lower limb edema and was dependent on home oxygen for multiple comorbidities which included systemic sclerosis, Sjögren’s syndrome, moderate pulmonary hypertension, progressive fibrosing non-specific interstitial pneumonia, osteoporosis, cyclophosphamide-induced cardiomyopathy (heart failure with preserved ejection fraction [HFpEF]), history of pulmonary embolism, and previous paraumbilical hernia repair. The patient’s lung function was declining, with multiple hospital admissions over the previous 2 years (fluid overload, chest infections, and pulmonary embolism). Medications for treatment of her comorbidities are listed in table 1.

Medication	Dose	Frequency
Fucidin ointment	-	PRN
Macitentan	10 mg	OD
Enoxaparin	60 mg	SQ Q 12 h
Pregabalin	75 mg	BID
Pirfenidone	543 mg	TID
Pantoprazole	40 mg	OD
Acyclovir	200 mg	Q 12 h
Sildenafil	25 mg	BID
Calcium and Vitamin D supplements	-	-
Dulcolax	-	PRN
Movicol	-	PRN

Table 1: On-board medications for comorbidities.

BID: Twice Daily, OD: Once Daily, PRN: As Needed, Q: Every, SQ: Subcutaneous, TID: Thrice Daily.

The patient was initially admitted to the intensive care unit (ICU) for septic shock secondary to a urinary tract infection (UTI) which required inotropic support. After UTI treatment was completed, the patient was transferred to hematology for further management. Initial laboratory findings are presented in table 2. Significant findings included elevated immunoglobulin A (IgA) kappa monoclonal protein (21 g/L) with an M spike in the β region, elevated kappa free light chain (162 mg/L), an elevated serum free light chain ratio (18; normal range: 0.26 - 1.65) and a high percentage (85%) of kappa light chain restricted bone marrow cells. Imaging revealed generalized decreased bone density with multilevel vertebral body collapse at D4, D7, D9, L1, and L5. No suspicious lytic bone lesions were seen. Magnetic resonance imaging (MRI) on 11 January 2020 showed multilevel, moderate to severe fractures in the thoracic and lumbar spine (Figure 1). There was heterogenous enhancement and increased signal intensity in the T4 vertebral body, which raised the possibility of a pathological compression fracture; there was no evidence of cord compression or plasmacytomas. The patient was diagnosed with stage II IgA kappa-restricted multiple myeloma and was not eligible for transplant due to her multiple comorbidities and low Karnofsky Performance Status.

Description	Patient's value
Blood/serum	
Hemoglobin	14.1 g/dL
White blood cell count	7.13 [x10E3/uL]
Absolute neutrophil count	2.93 [x10E3/uL]
Platelets	194000/ μ L
Erythrocyte sedimentation rate	140 [mm/hr]
Blood film	No abnormal cells seen
Activated partial thromboplastin time	47s
Prothrombin time	17s
Fibrinogen	4 g/L
Creatinine	85 μ mol/L
Calcium	2.7 mmol/L
β_2 microglobulin	2.6 μ g/mL
Lactate dehydrogenase	338 IU
Albumin	27 μ g/mL
Total protein	96 g/dL
Bence-Jones proteins	Positive
Infectious disease	
Hepatitis C	Negative
Hepatitis B	Negative
Human immunodeficiency virus	Negative
Liver function test	Normal
Renal function test	Normal
Hemantic	Normal
Serum protein electrophoresis	
IgA kappa monoclonal protein	21 g/L (M spike in β region)
Serum free light chain	
Kappa	162 mg/L
Lambda	9 mg/L
Serum free light chain ratio	18 (normal range: 0.26 - 1.65)
24h urine protein electrophoresis	
Total protein	1.1 g
Monoclonal protein	None detected
Bone marrow examination	85% kappa light chain restricted
Cytogenetics	Normal
FISH	
t(4;14)	Negative
t(14;16)	Negative
del(17p)	Negative
Immunophenotyping (bone marrow aspirate)	
Clonal plasma cells	19% (CD38 ⁺ , CD138 ⁺ , CD20 ⁺ , CD56 ^{dim} , kappa light chain restricted; CD19 ⁻ lambda light chain negative)

Table 2: Initial laboratory findings.
FISH: Fluorescent In Situ Hybridization.

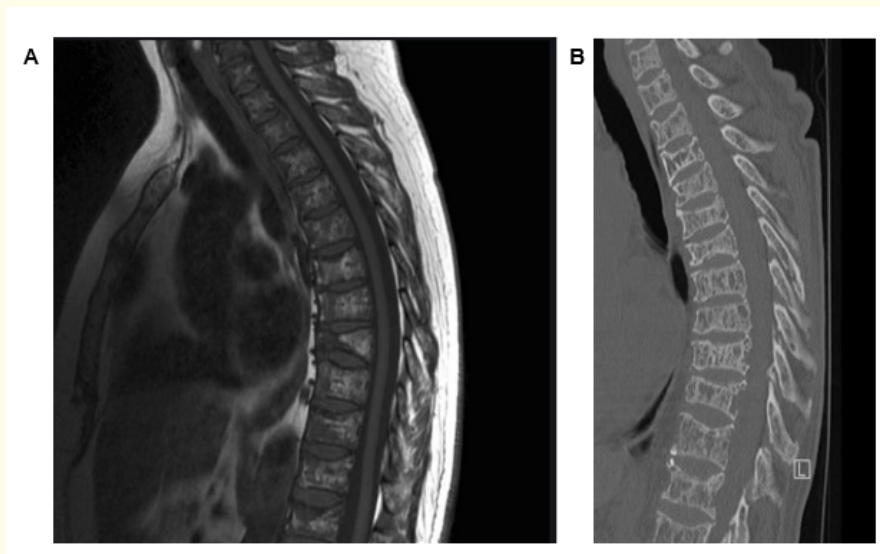


Figure 1: Initial MRI of thoracic and lumbar spine. (A) Thoracic spine. (B) Lumbar spine.
MRI: Magnetic Resonance Imaging.

The patient was prescribed radiotherapy (2000 cGy in 5 fractions to the T3-Si; dorsal and lumbar). The treatment started on 3 January 2020 and was completed on 3 May 2020 with no unintended interruptions or pauses. Due to the patient’s multiple comorbidities, all available chemotherapy treatment options were contraindicated. She was initially treated with bortezomib plus lenalidomide plus dexamethasone (VRD) starting on 9 January 2020. On D15 of treatment the patient was admitted with diffuse abdominal pain and subsequently diagnosed with intestinal obstruction; the patient underwent laparotomy and jejunal resection. Bortezomib and dexamethasone (lenalidomide was omitted due to risk of thrombosis) were restarted on 29 January, 2020 (D1 and D8; 28-day cycle). Treatment was interrupted on 25 February 2020 due to significant peripheral neuropathy with severe backache. A spinal MRI was negative for cord compression. The patient was given palliative radiotherapy for 5 days to control her back pain (initiated 05 March 2020; total dose, 80 Gy) which resulted in mild improvement. Treatment was changed from bortezomib to a modified protocol of low-dose carfilzomib plus dexamethasone (KD, Figure 2), which was initiated on 2 May 2020. The treatment regimen included zoledronic acid every D-1 and prophylactic acyclovir; granulocyte colony stimulating factor (G-CSF) or pegfilgrastim was given if needed. To date, the patient has completed seven 28-day cycles of treatment and continues on this regimen.

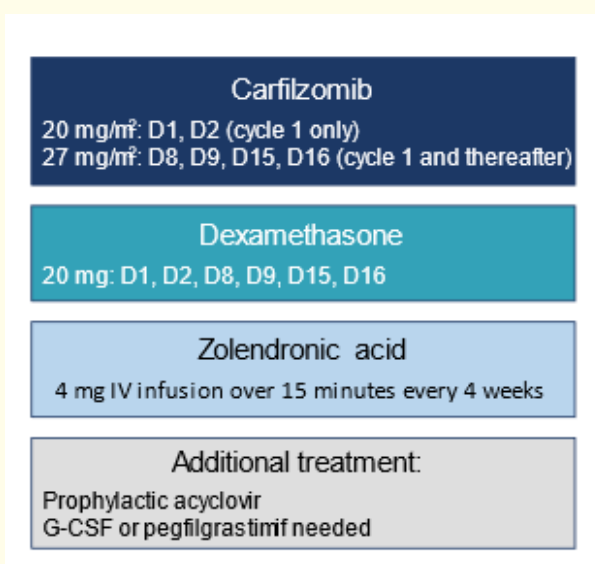


Figure 2: Modified low-dose carfilzomib plus dexamethasone treatment protocol (28-day cycle).
G-CSF: Granulocyte Colony Stimulating Factor.

Bone marrow biopsy after completing seven cycles of KD showed 7% plasma cells and flow cytometry was consistent with 1.6% clonal plasma cells (CD138⁺, CD117⁺ (partial), kappa light chain positive, lambda light chain negative). Decreases in serum IgA levels have been observed over the course of treatment (Figure 3A), with a drastic drop from the initial value of 18.70 g/mL to 4.52 g/mL in the second month of treatment. Levels have fluctuated between high and normal throughout her treatment; however, the three most recent readings (all in September 2020) were within the normal range. Kappa light chain levels also decreased over the course of treatment (Figure 3B). After seven cycles of modified low-dose carfilzomib plus dexamethasone, the patient showed partial remission in that the chemical light chain and bone marrow biopsy results had plateaued. A treatment regimen that was modified based on the patient’s comorbidities has resulted in clinical improvement.

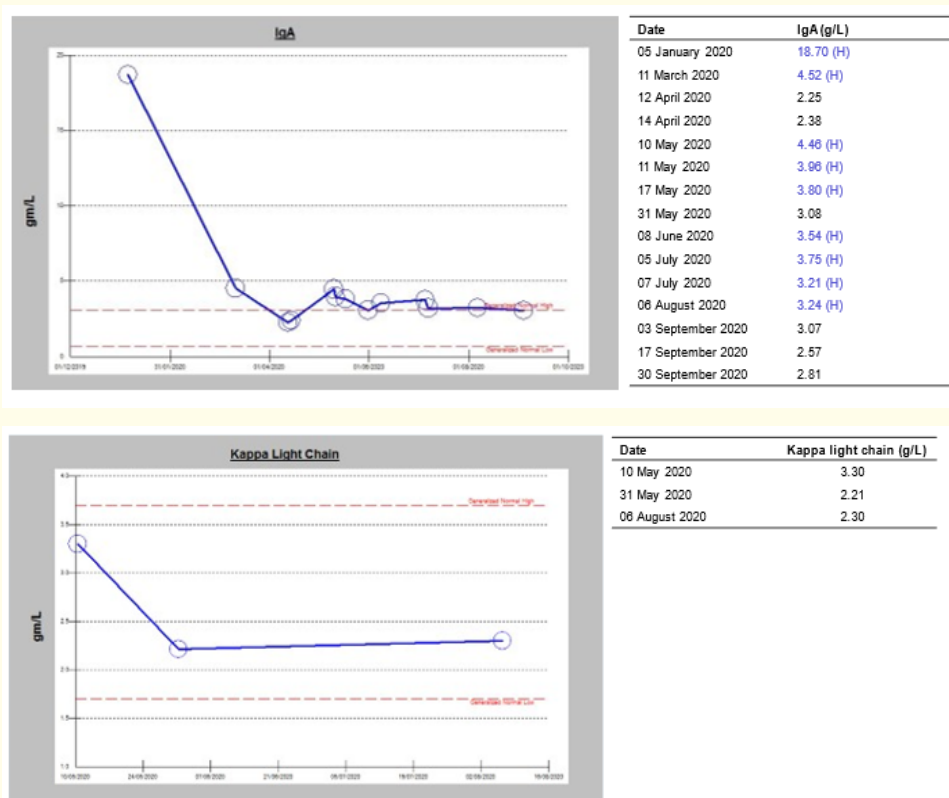


Figure 3: Changes in IgA and kappa light chain over time. (A) IgA. (B) Kappa light chain.

Discussion and Conclusion

A modified low-dose treatment regimen of carfilzomib plus dexamethasone has demonstrated clinical improvement in a patient with stage II multiple myeloma for whom all available chemotherapies were contraindicated. The modified treatment protocol was safe and well tolerated for up to seven treatment cycles and has demonstrated clinically meaningful efficacy.

Treatment options for this patient were limited due to her comorbidities. Additionally, she had moderate to severe pulmonary disease, which has been identified as an important variable for diminished overall survival in patients with multiple myeloma [9]. The patient ex-

perienced significant adverse events on VRD and bortezomib plus dexamethasone, so carfilzomib was used in place of bortezomib based on the findings of the ENDEAVOR study, which demonstrated that carfilzomib plus dexamethasone could be considered in patients with relapsed/refractory multiple myeloma for whom bortezomib plus dexamethasone is a potential treatment option [10]. Treatment in the ENDEAVOR trial consisted of 20 mg/m² on D1 and D2 of cycle 1 and 56 mg/m² thereafter [10]. Because of our patient's comorbidities, the dose was decreased to 27 mg/m², which was the lowest dose used in the ENDEAVOR trial (after dose reductions due to toxicity). This treatment decision was additionally supported by the results of a recent trial that demonstrated no significant differences in overall response rate, median progression-free survival, or median overall survival when patients with relapsed/refractory multiple myeloma were treated with low-dose (27 mg/m²) or high-dose (56 mg/m²) carfilzomib plus dexamethasone [11].

A study of older patients (≥ 65 years of age) with cancer reported that other outcomes, such as cognitive ability, were more important than survival [12]. This study highlighted the principle of “start low, go slow” in regard to cancer treatment. Conceptually, this principle encourages ongoing toxicity assessment and treatment adjustments, including dose reductions as needed to maintain quality of life for patients. Additionally, the authors noted that physicians should anticipate toxicities based on the drug used as they develop a treatment plan. These principles also apply to the present case study, as the patient had significant comorbidities. Lower dose intensity regimens are successfully used in older patients with multiple myeloma to improve the safety profile of treatment and to optimize treatment outcome [13]. The reason older patients benefit from lower doses is often related to reduced cardiac, pulmonary, renal, hepatic, and/or neurological function. This situation is similar to that of our patient, considering her numerous comorbidities.

Cardiovascular adverse events with carfilzomib in patients with multiple myeloma are incompletely characterized. A recent meta-analysis of clinical trial data reported an association of high-grade cardiovascular adverse events with carfilzomib at doses ≥ 45 mg/m² in phase 2 and 3 clinical trials [14]. Further studies are needed to clarify the cardiotoxic side effects of carfilzomib and to identify at risk patients. Additionally, studies to identify appropriate treatment modifications to achieve efficacy while mitigating the risk of cardiac events and to optimize monitoring for early signs of cardiovascular adverse events while on treatment are warranted.

Modified treatment regimens should be considered when conventional treatment is contraindicated or not well tolerated. Close monitoring for adverse events and evidence-based adjustments to dose and/or treatment agents can facilitate the safe and effective use of modified treatment regimens.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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