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Case Report

Carfilzomib: A cause of drug associated thrombotic microangiopathy

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ABSTRACT

Carfilzomib is a selective proteosome inhibitor approved for treatment of relapsed and refractory multiple myeloma. Recent reports have linked exposure to carfilzomib with development of thrombotic microangiopathy (TMA). We describe two cases of biopsy proven thrombotic microangiopathy that occurred after the initiation of carfilzomib (dosed at 32 mg/m^2 and 23 mg/m^2, respectively) for relapsed multiple myeloma. Both patients were managed with discontinuation of the drug, therapeutic plasma exchange (TPE) and supportive care. Hemoglobin, platelets and renal function did not improve with TPE. TMA resolved with creatinine returning to baseline several weeks after discontinuation of the drug. The outcomes suggest that TPE is not beneficial for treating carfilzomib-induced TMA.

1. Introduction

Thrombotic microangiopathy (TMA) is a feature of numerous clinical conditions including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulopathy, malignant hypertension and cancer [1]. Certain medications (e.g. quinine, ticlopidine, gemcitabine) have also been implicated as causative agents [2]. TMA is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and microvascular thrombi usually in the setting of renal failure [3].

Therapeutic plasma exchange (TPE) is often used as a therapy for TMA. Some indications are known to respond very well to this intervention with significant improvement in morbidity and mortality (e.g. TTP). However, other indications show variable response (e.g. atypical HUS, drug-induced TMA) or no response (e.g. DIC, malignant hypertension) to TPE [4].

The proteasome inhibitor, bortezomib, has been approved to treat patients with relapsed and refractory cases of multiple myeloma (MM). Several cases of bortezomib-induced TMAs have been reported in the medical literature [5–9]. Typical treatment included withdrawal of drug and supportive care. Patients who were also treated with plasma infusion or TPE had variable recovery of renal function or hematologic factors based on these interventions [5,7,8].

Carfilzomib, a second-generation proteasome inhibitor, was approved for the treatment of relapsed and refractory multiple myeloma by the US Food and Drug Administration in 2012 [10]. This second generation drug provides robust and durable responses with a preferable safety profile when compared to the first generation drug, bortezomib [11]. The safety data of carfilzomib from 4 phase II clinical trials, representing over 500 patients, showed that hematologic adverse events (AE) were experienced in a majority of patients with anemia and thrombocytopenia accounting for 47% and 38% of AE, respectively. Acute renal failure was noted in 5% of patients but no documentation

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of TMA with associated renal failure was described [11]. However, recent publications have implicated carfilzomib as a causative agent of drug-induced TMA [12,13]. In this report, we present two cases of biopsy proven TMA and acute renal failure in patients with relapsed MM that were treated with carfilzomib. Both patients failed to respond to daily TPE, but experienced resolution of hematologic and renal function several weeks after discontinuation of the drug.

2. Methods

Patients with multiple myeloma (not described in this report) who were undergoing treatment with carfilzomib had peripheral blood plasma collected for von Willebrand factor (vWF) multimer testing. The Mayo Clinic Institutional Review Board approved this study and patients signed informed consent prior to sample collections. The research was conducted in accordance to the principles of the Declaration of Helsinki. Samples were sent to the clinical laboratory where a standard vWF multimers assay was done (agarose gel electrophoresis/infrared dye-labeled antibody detection) [14].

3. Case Reports/Results

Patient 1 was a 73-year old Caucasian male diagnosed MM in 2001. His past medical history is significant for type 2 diabetes mellitus, chronic hypertension and prostate cancer. The patient was initially treated with thalidomide and dexamethasone. He received an autologous stem cell transplant in August 2002 followed by complete remission. In 2010, the patient relapsed and sought alternative stem cell therapies outside of the United States. He continued to progress and was subsequently treated with bortezomib, cyclophosphamide and dexamethasone starting in 2012. The patient developed severe neuropathy from bortezomib and this drug was stopped. In 2014, the patient received two cycles of carfilzomib. Pre-carfilzomib treatment, baseline laboratory parameters are noted in Table 1. After the second cycle of carfilzomib, the patient was admitted to the hospital with fatigue, generalized weakness and hypertension with systolic blood pressure >170 mmHg. He was found to have anuric acute kidney injury (AKI) with a creatinine 5.9 mg/dl, thrombocytopenia and elevated LDH. Although the patient was not anemic, the peripheral blood smear showed 3–5 schistocytes per high-powered field. The patient underwent a kidney biopsy that demonstrated subacute TMA and glomerular basement membrane injury.

The clinical and laboratory findings were suggestive of drug-induced TMA and a trial of TPE was initiated. The patient underwent daily TPE, exchanging 1 plasma volume with thawed plasma. There was no improvement in platelet counts or renal function during the exchange. Of note, this patient was transfused with platelets prior to initiation of TPE. The pre-TPE series platelet count was 37×10^3/uL and after 5 consecutive TPE, the platelet count remained the same. The patient's hemoglobin dropped from 9.9 g/dL before initiating TPE to 7.4 on day 4 of TPE, he was transfused with RBC and platelets at this time, but no measurable response to the platelet transfusion was observed. After stopping TPE, the patient's platelet count gradually increased to 77×10^3/uL over the next week. His pre-TPE creatinine was 6.6 mg/dL and only marginally decreased to 6.4 mg/dL after the TPE series. The patient received intermittent hemodialysis for 5 weeks until he started to autodiurese with stable creatinine at 1.6 mg/dl.

Patient 2 was a 72-year old Caucasian female who was diagnosed MM in 2007. Her past medical history is also significant for chronic hypertension that was well controlled on medical therapy. Initial treatment for MM consisted of lenalidomide and dexamethasone. The patient received autologous stem cell transplant in 2008, but relapsed in 2010. She was then treated with bortezomib, which was discontinued because of intolerance. Lenalidomide and dexamethasone were reinitiated, but this regimen also had to be stopped due to adverse side effects including multiple episodes of syncope, vitreous hemorrhage and pneumonia. Next, the patient was treated with six cycles of carfilzomib. Her baseline laboratory values are noted in

Table 1
Baseline, admission, pre- and post-TPE laboratory values.

	Baseline	Admission	Pre-TPE	Post-TPE	Normal range
Patient 1					
Hemoglobin	15.4	14.7	9.9	9.8	12.0–15.5 g/dL
Platelets	123	23	37[a]	40	149–375 × 10^3/uL
Creatinine	1.0	5.9	6.6	6.4	0.6–1.1 mg/dL
eGFR	>60	9.5	8.3	8.6	>60 mL/min
LDH	201	2192	ND	576	122–222 U/L
ADAMTS-13	ND	50	ND	ND	>70%[b]
Patient 2					
Hemoglobin	9.8	8.7	8.3	10.7[a]	12.0–15.5 g/dL
Platelets	153	24	104[a]	59	149–375 × 10^3/uL
Creatinine	1.4	1.8	2.0	2.1	0.6–1.1 mg/dL
eGFR	49.0	34.1	24.5	18.9	>60 mL/min
LDH	285	650	ND	363	122–222 U/L
ADAMTS-13	ND	91	ND	ND	>70%[b]

Pre-TPE = results reported < 12 hour prior to initiating TPE; Post-TPE = results reported <24 hours after the last TPE.
eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; ND, not determined.
[a] Post-transfusion values.
[b] ADAMTS-13 activity levels in TTP are <10%.