Carfilzomib-Related Acute Kidney Injury

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Background

Carfilzomib (Kyprolis, Onyx) is a next-generation epoxyketone proteasome inhibitor that is approved for the treatment of relapsed refractory multiple myeloma.[1] The phase 2 trial[2] that initially raised interest in this agent was a single-arm study of patients with refractory multiple myeloma who received carfilzomib 20 mg/m^2 intravenously twice weekly for 3 weeks in cycle 1 and then 27 mg/m^2 for subsequent cycles. Increased serum creatinine was the most frequently reported renal adverse event, affecting 25% of the 266 patients in this study.

The National Institutes of Health and the National Cancer Institute use the same terminology and grading system to describe adverse events with chemotherapy agents. Grade 1 injury refers to a creatinine level 1.5 to 2.0 times above baseline or a creatinine level increase of greater than 0.3 mg/dL. Grade 2 injury refers to a creatinine level 2.0 to 3.0 times above baseline. Grade 3 injury refers to a creatinine level more than 3.0 times above baseline, or above 4.0 mg/dL with need for hospitalization. Grade 4 injury refers to life-threatening injury requiring dialysis, and grade 5 injury means death. In the phase 2 trial with carfilzomib,[2] the majority of the renal adverse events were grade 1 or 2 in severity, and none led to discontinuation of carfilzomib. Acute kidney injury was reported in 13 patients (5%), 9 of whom experienced serious grade 3 acute renal failure. Chronic renal failure was reported in 10 patients (3.8%), with 3 of these events considered severe and 2 resulting in discontinuation of carfilzomib.[2]

Case Report

We report a case of acute kidney injury (grade 3) after administration of carfilzomib. A 68-year-old man with IgG κ-type refractory multiple myeloma presented to the hospital with fever and acute-on-chronic kidney disease (creatinine 3.65 mg/dL, baseline 1.6 mg/dL). He had been switched to carfilzomib and steroids 1 month prior to presentation because his disease had failed to respond to bortezomib and thalidomide, and had received 1 cycle of carfilzomib and dexamethasone 9 days prior to presentation.

His vital signs on presentation were a blood pressure of 128/72 mm Hg, heart rate of 82 beats per minute, respiratory rate of 14 breaths per minute, and temperature of 36.7°C. His physical examination revealed no signs of volume depletion or overload. No rashes were noted on skin examination. During the hospital course, his creatinine peaked at 4.59 mg/dL but slowly improved to 2.0 mg/dL after cessation of carfilzomib.

Prior to administration of carfilzomib, his free κ:λ ratio was 78. His renal function worsened as the κ:λ ratio decreased to 16.8, suggesting that multiple myeloma was not the cause of the renal injury. His serum calcium was in the range of 8.5 to 9.0 mg/dL. His uric acid was normal. Urinalysis revealed a urine pH of 6, a specific gravity of 1.009, mild glycosuria, a small amount of blood, 75 mg/dL of protein, 2 to 5 white blood cells per high power field, and 0 to 2 red blood cells per high power field. No granular, red blood cell, or white blood cell casts were noted. His proteinuria was unchanged, at 1.6 g per 24 hours. No significant hypotension, no other nephrotoxic agents, and no signs of postrenal obstruction were found on further evaluation. His renal function continued to improve slowly after cessation of carfilzomib.

No carfilzomib challenge was performed given the concern of further kidney injury, and no kidney biopsy could be performed owing to thrombocytopenia. Despite this, we considered carfilzomib to be the most probable cause of the acute injury based on the timing of the administration of the chemotherapy agent in relation to the injury and on the scoring system used in the Naranjo Adverse Drug Reaction Probability Scale.[3]

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Discussion

Although serum creatinine elevation was reported in initial trials of this agent, no published case reports exist that suggest this association. The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)[4] is a database managed by the FDA for online voluntary reporting of adverse drug events by health care professionals and consumers. We examined the FAERS database using the term *carfilzomib* plus 1 of the following other terms as search criteria: *renal failure, renal failure acute, blood creatinine increased, acute kidney injury, acute renal failure, elevated creatinine,* and *nephrotoxicity*. We discovered 6 additional reports from January 2012 through December 2012.

We believe that carfilzomib carries a risk of nephrotoxicity. As a result, we recommend that all patients taking this agent should have their renal function monitored closely, and that carfilzomib be used with caution in patients with compromised renal function. Given that this agent is used in refractory multiple myeloma patients, who often develop chronic kidney disease, the risk could be higher than originally postulated.

The mechanism of the kidney injury in this patient remained unclear. One possibility was transient prerenal or tubular injury. The proteinuria in this patient was unchanged from the time multiple myeloma was originally diagnosed. Hypercalcemia and/or tumor lysis syndrome were unlikely to have caused the kidney injury in our patient.

In a patient who has multiple myeloma with renal involvement, nephrotoxicity caused by the disease can be hard to distinguish from nephrotoxicity caused by an agent. Our report of the above case emphasizes risk of renal toxicity with the newest generation of proteasome inhibitors.

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Commentary

Treatment of Multiple Myeloma With Carfilzomib in Patients With Renal Injury

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Carfilzomib is a next-generation proteasome inhibitor recently approved for the treatment of relapsed/refractory multiple myeloma (RRMM). It is an epoxyketone that selectively inhibits the chymotrypsin-like activity of the proteasome.[1] In a phase 2 study of single-agent carfilzomib in 266 patients with RRMM, an overall response rate of 23.7% and a median progression-free survival of 3.7 months were observed.[2]

Patients with MM are affected by many complications of the disease, including renal impairment. Approximately 20% of MM patients have been shown to develop renal failure during the course of the disease.[3,4] Among patients with renal failure, those who do not recover renal function have shorter survival than those who do,[3] which demands that effects on renal function be considered with new therapies. With the recent approval of carfilzomib, the safety profile of the drug is of substantial interest, including the possibility of treatment-emergent renal adverse events.

In this case report, Jhaveri and colleagues present a case of grade 3 acute kidney injury in a patient that occurred 9 days after having received 1 cycle of carfilzomib and dexamethasone.[5] The patient was previously refractory to bortezomib and thalidomide treatment. The patient's creatinine at baseline was 1.6 mg/dL, which increased to 3.65 mg/dL at the onset of the adverse event, peaked at 4.59 mg/dL, and slowly improved to 2.0 mg/dL after cessation of carfilzomib and continuation of supportive

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measures. The report suggests the possibility of a relation between the adverse event and carfilzomib, and a potential need for caution in use of the drug in patients with compromised renal function.

Badros and colleagues[6] specifically compared the pharmacokinetics and safety of carfilzomib among MM patients in several predefined cohorts identified by various degrees of renal function (creatinine clearance >80 mL/min, 50-80 mL/min, 30-49 mL/min, and <30 mL/min; and chronic hemodialysis). The researchers studied 50 patients with RRMM who had disease progression after 2 or more prior lines of therapy, and observed no differences between patients with and without normal renal function in carfilzomib clearance and exposure. Adverse events, including renal dysfunction, were similar among all groups.

Similarly, Siegel and colleagues reported an analysis of renal dysfunction in 526 patients treated with single-agent carfilzomib in 4 phase 2 trials. At baseline, 23.8% of the patients had moderate to severe renal dysfunction and 39.4% had mild renal dysfunction. Just more than half—51%—experienced progression of disease after carfilzomib treatment. The analysis showed that overall, 87% of patients did not have worsening renal function during treatment. Of the patients who experienced worsening of renal function, 46% experienced transient worsening of a median duration of 1.4 weeks, and 54% experienced nontransient worsening. A total of 8 of the 37 patients with nontransient worsening discontinued carfilzomib treatment owing to an adverse event related to renal dysfunction. Most of them had progressive myeloma, much like the patients in the Badros study.

Although the case presented by Jhaveri and colleagues raises an important issue to consider regarding the use of carfilzomib in MM patients, the literature on the subject yields the general conclusion that the use of the drug does not significantly increase renal injury. The initial experience with carfilzomib obtained from the original phase 1 and 2 trials suggests that several factors are involved in the development of renal signal. Tumor lysis syndrome upon initiation of carfilzomib, cytokine storm with capillary leak syndrome, and progressive myeloma are all factors associated with kidney injury.[2] The renal signal reported in the large experience by Siegel and colleagues[7] suggests that transient events likely obey a poorly understood vascular process, whereas progressive myeloma is more common in the majority of cases that present with a nontransient signal.

Although it remains challenging to determine the cause of the acute kidney injury in this particular patient, the consideration of additional information about the case would be helpful. First, information on the creatinine levels at the time of administration of the first 6 doses of carfilzomib in the first cycle would allow for analysis of the immediate effect of the drug on renal function. As a note, the development of renal failure 9 days after 1 full cycle suggests that other causes may have been responsible, and the lack of rechallenge also makes the confirmation of cause very difficult. In addition, information on other measures taken to treat the adverse event besides the cessation of carfilzomib is necessary to consider. The raw κ and λ free light chain values before therapy, during treatment, and during the adverse event should be reported as well, and the value for proteinuria should be reported as separate values of albumin and light chain (Bence-Jones protein).

Analysis with additional information as suggested will allow possible causes to be further dissected. We would be interested in evaluating, serially and prospectively, cohorts of patients receiving predefined carfilzomib doses, and functionally and histologically reexamining those who show renal alteration during and after exposure to the drug. It should be noted, however, that this is just one instance, and studies examining large patient populations have not concluded any significant direct nephrotoxic effects of carfilzomib. Yet if repeated events of renal toxicity occur that could be attributed specifically to carfilzomib, the reexamination of the renal safety profile of the drug will be necessary.

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