CLINICAL VIGNETTE

Acute Kidney Injury Related to Repeated Oxaliplatin Use

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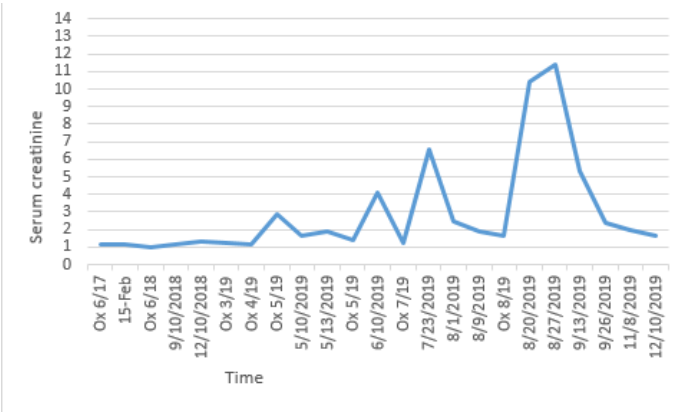
Case Presentation

A 73-year-old man was referred to nephrology for worsening renal function. He has Type 2 Diabetes Mellitus, Essential Hypertension, Hyperlipidemia and known colorectal cancer which was initially diagnosed more than 10 years ago. He was initially treated with FOLFOX (Leucovorin, Fluorouracil, and Oxaliplatin) followed by surgical resection. A solitary liver metastatic lesion was noted a year after surgery which was tested with radio frequency ablation. Abdominal wall drop metastases were noted 5 years status-post surgical resection. Five years later his cancer recurred with biopsy proven pericardial and pleural lesions. He restarted initial treatment with XELOX (Oxaliplatin and Capecitabine), and switched to Bevacizumab (Avastin) and later Capecitabine (Xeloda). His CEA increased with evidence of slow progression, and Oxaliplatin was added back to his regimen several months later. His baseline creatinine was around 1.1 to 1.3, but worsened immediately after his chemotherapy infusions with Oxaliplatin and Bevacizumab, with creatinine improving back to baseline within a few days. However, six months after starting this regimen he had an episode of AKI while only taking Oxaliplatin.

His episodes of AKI were presumed to be pre-renal and were treated with IV hydration. There was no hydronephrosis seen on renal ultrasound and he did not have recent exposure to iodinated contrast. It was initially thought that the Bevacizumab might be causing the AKI, however despite holding the Bevacizumab he continued to have worsening AKI on Oxaliplatin alone which resulted in hospitalization. His serum creatinine increased to 11.5 mg/dL, with BUN 144, calcium 8.2, potassium 5.5. WBC 7.9, Hemoglobin 9.1 and Platelets 80K. Urinalysis showed specific gravity <1.005, trace protein, moderate blood, 0-2 RBCs, 0-2 WBCs, and spot urine protein creatinine ratio was 0.4 g. Patient was free if uremic symptoms and did not have any emergent indication for dialysis. He responded well to IV hydration and kidney ultrasound was again unremarkable without hydronephrosis. Kidney biopsy showed mild to moderate acute tubular injury and mild arterial and arteriolar nephrosclerosis. The acute tubular injury felt to be most likely medication induced and there was no thrombotic microangiopathy. His serum creatinine slowly improved during the hospitalization and he was discharged home with serum creatinine of 7.2 mg/dL.

Graph showing creatinine elevation in response to Oxaliplatin administration. Ox= Oxaliplatin. Serum creatinine in mg/dL.



Discussion

Oxaliplatin is a third-generation platinum compound, with cytotoxic activity against different solid tumors including colorectal cancer, especially in combination regimens with 5-fluorouracil. Oxaliplatin was developed to decrease risk of cisplatin nephrotoxicity. Oxaliplatin pharmacokinetics differs from cisplatin with low-plasma accumulation and renal elimination via simple glomerular filtration without tubular metabolism.[1]

The most common adverse effects are neuropathy, nausea, vomiting, and hematologic toxicity. Oxaliplatin has renal clearance but renal side effects remain unclear. With increasing use of Oxaliplatin, there have been an increasing number of AKI cases reported. The pathogenesis in most cases of Oxaliplatin-induced AKI is acute tubular necrosis (ATN) confirmed by kidney biopsy.

Literature review shows few case reports of severe AKI after the use of Oxaliplatin.[2,3] In previous reports of Oxaliplatin-induced AKI, the clinical syndrome was associated with gross hematuria, thrombocytopenia, thrombotic microangiopathy (TMA),[4,5] and one case of severe symptomatic hemolytic anemia.[5] In our case, hematological abnormalities were

thrombocytopenia and anemia, attributed to renal failure and medular toxicity, without any signs of hemolysis or TMA. AKI rarely occurs after Oxaliplatin treatment alone and, while often severe, is potentially reversible. Our patient, had progressive worsening renal failure with each Oxaliplatin treatment. Oxaliplatin was very likely responsible for AKI in our patient, as there was a close temporal relationship between drug treatment and onset of renal failure. It is also unclear whether our patient's prolonged exposure to Oxaliplatin placed him at a higher risk of AKI. While prolonged exposure has been implicated as a risk factor for Oxaliplatin dependent immune-mediated hemolysis, previously reported cases of Oxaliplatin induced ATN have been observed after as few as four cycles of treatment.

Aggressive measures are needed to avoid severe AKI including close monitoring of labs and hydration. When the clinical picture is atypical, kidney biopsy should be performed. As with previously reported cases, our patient eventually recovered the majority of his renal function with creatinine returning to 1.17.

Conclusion

Oxaliplatin treatment typically causes hematological abnormalities including leukopenia, thrombocytopenia, hemolysis and TMA. Oxaliplatin-induced AKI is a rare but serious complication of the commonly used FOLFOX chemotherapy regimen. Physicians should be aware of this since management of TMA requires plasma exchange therapy in addition to supportive therapy of AKI. A kidney biopsy should be considered when the clinical picture is atypical which would help with deciding therapy and establish prognosis.

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