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Renal Pelvic Hemorrhage and Acute Renal Failure Associated with Carboplatin Therapy

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Abstract

A 44-year female with ovarian cancer and normal renal function developed gross hematuria following carboplatin therapy. Laboratory investigation revealed elevated BUN and serum creatinine. CT scan of abdomen and pelvis with or without contrast revealed bilateral hydronephrosis with high attenuation material within the left renal pelvis and both ureters consistent with blood. Delayed images at 3 hours revealed intense nephrogram with delayed excretion of contrast bilaterally. She underwent cystoscopy and placement of ureteral stent bilaterally. She had brisk diuresis with associated progressive decrease in serum creatinine to baseline value.

Keywords

Renal hemorrhage; ARF; Carboplatin

Introduction

Platinum analogues have become mainstay of treatment for many tumors including ovarian, lung, germ cell, head and neck, bladder and to a lesser degree breast and gastric. Cisplatin was the first platinum analogue introduced into clinical trials in 1972 as tumoricidal agent.¹ In view of its substantial side effects, including nausea, vomiting, renal dysfunction, neuro and ototoxicity, second generation of platinum compounds were developed. Carboplatin is one of the second generation platinum compounds with more or less similar spectrum of activity but with less toxic profile. Carboplatin has been reported to offer benefit of reduced GI and renal side effects, allowing an ease of outpatient administration and obviating the need for hydration and anti emetic therapy. We report a case of acute renal failure and gross hematuria associated with carboplatin use in a patient with ovarian carcinoma.

Case Report

A 44-year-old African American female presented to emergency room (ER) with one-day history of gradually progressive gross hematuria with clots. This was associated with suprapubic and left flank pain. She also complained of burning on passing urine. She denied any fever, chills or trauma. She had not noticed any decrease in urine output prior to coming

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to the hospital. Her past medical history was significant for recently diagnosed ovarian carcinoma. The ovarian lesion had been picked up during a CT scan done to evaluate abdominal pain following a skiing accident a month prior to current hospital visit. No abnormalities in the kidneys were detected on the CT scan. Following this she had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy. Thirty-six hours before the onset of her symptoms she had received her first cycle of chemotherapy. This included carboplatin 792 mg in 250 ml normal saline for an area under the curve (AUC) of 6 and paclitaxel 292 mg (175 mg/m²) in 500 ml normal saline. She also had history of hypertension for which she was not on any treatment. In addition, she had undergone myomectomy for uterine fibroids. She was on decadron 8 mg/day. She denied smoking cigarettes or tobacco use in the past.

Examination was significant for healing surgical scar over the abdomen along with suprapubic and left costo-vertebral angle tenderness. Rest of the examination was unremarkable. Initial lab work was significant for a serum creatinine (Scr) of 0.7 mg/dl, WBC count of 7.91×10^3 /ml, Hemoglobin 11.8 g/dl and platelet count of 287,000. Urine analysis was significant for large blood. Microscopic examination of urine revealed 0–2 WBCS and too numerous to count RBCS/high power field. She was started on aggressive intravenous hydration with normal saline (150 ml/hour). Over the first 24 hours while in the hospital, her urine output was noted to decrease and her serum creatinine increased to 2.8mg/dl. CT scan of the abdomen and pelvis with and without intravenous contrast revealed bilateral hydronephrosis with high attenuation material within the left renal pelvis and both ureters consistent with blood. Delayed images at 3 hours revealed intense nephrograms with delayed excretion of contrast bilaterally. This was suggestive of blood clots in both ureters causing hydronephrosis and leading to acute renal failure (see Figure 1). CT scan did not reveal any renal mass, cystic kidney disease or urinary tract calculi.

She was taken to operating room where she underwent cystoscopy with placement of ureteral stents bilaterally. She had brisk diuresis with associated progressive decrease in serum creatinine to 0.6 mg/dl over the next five days. She had a normal diuretic renal scan, a day after she underwent ureteral stents placement. She did not undergo any further imaging of her kidneys as her serum creatinine continued to be in normal range. Urine cytology was negative for malignant cells.

Discussion

Cisplatin is a complex of platinum surrounded by two ammonia molecules and two chloride ions in the Cis position. In carboplatin, cyclobutane bidentate side chains replace the two chloride ions. These changes in structure are responsible for carboplatin's different systemic pharmacology and toxicity profile. Unbound carboplatin has a half-life between 3 to 6 hours with 60–80% eliminated by the kidneys. The drug is 20–40% bound to plasma proteins.² Both cisplatin and carboplatin undergo glomerular filtration and tubular reabsorption, but only the kidneys retain less of carboplatin. Inside the cell, platinum compounds react with DNA or other nucleophilic site only after at least one ligand is replaced by water (Chloride for cisplatin and cyclobutane bidentate ligand for carboplatin).

At the commonly employed dose schedules renal failure is reported to be uncommon with carboplatin compared with 5–10% occurrence with cisplatin use. In earlier reports using high dose carboplatin (800 mg/m²), there was a decrease in creatinine clearance (36–61%) from baseline in three patients who received the medications without hydration. Hydration with normal saline at 250ml/hour for 6 hours (3hours before and 3 hours after carboplatin) in nine additional patients did not result in any decrease in the creatinine clearance. All these twelve patients had received cisplatin before and were reported to have preexisting stable cisplatin related renal dysfunction.³

Acute renal failure due to carboplatin is rare; despite a reported fall in glomerular filtration rate (GFR) greater than 25% in a phase I dose escalation study.⁴ The risk of nephrotoxicity increases with concomitant administration of aminoglycosides. In a study by Rosell et al comparing paclitaxel and carboplatin with paclitaxel and cisplatin in patients with advanced non-small cell lung cancer, 15% had some form of renal dysfunction while only 1% had grade 3 nephrotoxicity.⁵ In another study by Du Bois et al involving paclitaxel/carboplatin in treatment of ovarian cancer, 5.4% of the subjects were noted to have grade 1 or 2 nephrotoxicity.⁶ McDonald et al reported 2 cases of acute renal failure following intraperitoneal use of carboplatin.⁷ Both these patients had kidney biopsy findings consistent with acute interstitial nephritis. They had received multiple cycles of cisplatin and carboplatin prior to developing acute renal failure. In a more recent report, Ozguroghu presented a 71-year-old woman who went into acute renal failure requiring dialysis after receiving 14 cycles of paclitaxel and carboplatin over several months.⁸

Hematuria with carboplatin use is a less recognized complication. Ettinger et al first reported 2 episodes of hematuria in the same patient following carboplatin use. Unfortunately this patient had associated thrombocytopenia at least during one of these episodes. On the second occasion, it was presumed to be secondary to hemorrhagic cystitis and the patient did not undergo cystoscopy.⁹ Agraharkar reported a 57-year-old woman with ovarian cancer who developed gross hematuria with acute renal failure after receiving carboplatin and paclitaxel. Renal function and urine output improved with intravenous hydration. Intravenous pyelogram revealed filling defects in the ureter suggestive of bleeding.¹⁰

Our patient received the standard dose of carboplatin for an AUC of 6 and paclitaxel. She did not receive any intravenous hydration, as it is not part of standard protocol currently. Thirty-six hours after receiving chemotherapy, she developed gross hematuria with clots. This led to acute renal failure secondary to obstructive uropathy as evidenced by bilateral hydronephrosis necessitating bilateral ureteral stent placement. Unlike in prior reports of acute renal failure associated with carboplatin use, she had not received cisplatin or carboplatin previously.

The exact mechanism of injury is unknown. We believe that it is likely to be due to direct toxic effect of carboplatin on the transitional epithelial cells. Given the fact that renal dysfunction is not uncommon with carboplatin use and consequences of acute renal failure can be devastating requiring renal replacement therapy or surgical interventions, it may be prudent to aggressively hydrate the patients receiving carboplatin similar to that employed when using cisplatin to avoid this toxicity.

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Figure 1. CT scan with contrast showing clots in the pelvis (A) and ureter (B) as filling defects indicated by arrows. CT scan without contrast showed clots in the pelvis (C) and ureter (D) as indicated by arrows.