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CLINICAL VIGNETTE

Acute Renal Failure Associated with Administration of Ifosfamide

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Case report:

A 39-year-old woman presented to her primary care physician complaining of pain in her low back and flanks. She was initially treated with non-steroidal anti-inflammatory medications with no improvement in her symptoms. MRI of her lower back and pelvis revealed a pelvic mass with extension to the uterus. The patient underwent hysterectomy and pelvic mass resection. The pathologic evaluation of the mass revealed dedifferentiated liposarcoma with a colonic mesentery origin.

The patient was admitted to the hospital for recurrence of severe lower back and flank pain four weeks after her hysterectomy and pelvic mass resection. Imaging studies of the abdomen and pelvis revealed the recurrence of the tumor. The patient was initiated on a 7-day infusion of ifosfamide chemotherapy. Before ifosfamide was initiated, the patient's serum creatinine was 0.7 mg/dl and her BUN was 7 mg/dl. Microscopic examination of the urine was normal. Four days after the ifosfamide therapy was completed, the patient had an elevation in her creatinine to 2.0 mg/dl and a urine test positive for blood and protein.

Over the course of treatment with ifosfamide, the patient developed oliguria, peripheral edema and symptoms of fluid overload. She also developed a decreased level of consciousness felt to be encephalopathy related to ifosfamide. Because of these symptoms and her declining kidney

function, her ifosfamide therapy was stopped on day 4 of her chemotherapy infusion. By day 8 her serum creatinine had risen to 4.0mg /dl and her estimated glomerular filtration rate (GFR) was 14 ml/min. Her oliguria worsened, and she developed proteinuria, increased edema, and signs of increased intravascular volume and worsening of renal function over the next 2 to 3 days. Hemodialysis was started and a diagnosis of ifosfamide acute kidney injury was considered. The patient's acute kidney injury evaluation did not reveal any other etiology. Ultrasound guided kidney biopsy revealed severe acute tubular necrosis.

Discussion:

Ifosfamide is an alkylating chemotherapeutic agent that is used concurrently with other drugs to mainly treat some sarcomas and germ-cell tumors. It is a structural isomer of cyclophosphamide and it requires biotransformation to become cytotoxic. The metabolism of ifosfamide results in formation of metabolites including, 4-hydroxy-ifosfamide (activated ifosfamide), and Chloroacetylaldehyde (CAA). The latter is believed to be associated with central nervous system toxicity and nephrotoxicity¹.

Renal toxicity of ifosfamide manifests as tubular and glomerular dysfunction. The tubular dysfunctions associated with ifosfamide nephrotoxicity are manifold and include the following: renal glucosuria, aminoaciduria, tubular proteinuria, increase in beta-2-microglobulin excretion, Fanconi

syndrome, normal anion gap metabolic acidosis renal tubular acidosis type 1 (distal) and type 2 (proximal), hypophosphatemia secondary to decreased proximal tubular phosphate reabsorption and consequent phosphaturia, and polyuria secondary to nephrogenic diabetes insipidus. Reduction in glomerular filtration rate is usually mild unless ifosfamide is given in high dose or combination with other nephrotoxins. Risk factors for ifosfamide nephrotoxicity include the cumulative dose (cumulative doses of 45g/m² and above), previous or concurrent cisplatin treatment, and unilateral nephrectomy^{2,3}.

The mechanism of ifosfamide-induced nephrotoxicity is believed to be through inhibition of oxidative phosphorylation at the level of complex I of the mitochondrial respiratory chain by its metabolite chloroacetaldehyde CAA⁴. This effect has been shown to be prevented by agmatine which enhances mitochondrial oxidative phosphorylation and beta oxidation⁵. Inhibition of complex I results in decreases in total glutathione and cellular ATP levels which in turn cause cell necrosis. An in vitro study of the effect of CAA on human proximal tubule cells shows that CAA directly reacts with cellular protein and non protein thiols, lowers the levels of glutathione (GSH) in the cells, and mediates its toxicity on the cells. The lowering effect of CAA on intracellular GSH can be prevented by N-acetylcysteine (NAC). In-vitro study of porcine renal proximal tubular cells concurrently treated with NAC and IFO revealed higher level of cellular viability compared to the cells that were not treated with NAC. Higher levels of viability also correlate with significantly higher level of intracellular and total GSH levels in cells receiving concurrent treatment of NAC⁶.

It has also been shown that urinary acidification can attenuate the lowering effect of CAA on intracellular GSH and urinary acidification can be considered as an option to prevent IFO nephrotoxicity⁷. Forced diuresis and alkalization of urine

been suggested to prevent the urological complications associated with IFO. These complications have been attributed to IFO metabolite, Holoxan that mainly affects the supravescical areas. (tubulopyelo-ureteritis)⁸.

Conclusion

Ifosfamide is a commonly used alkylating chemotherapeutic agent that is mainly used in patients with sarcoma and refractory lymphoma. Acute kidney injuries presenting as tubular and glomerular diseases are associated with ifosfamide. Patients with ifosfamide nephrotoxicity may not completely recover from their acute kidney injuries and can end up with some degree of chronic kidney disease. Many studies have shown that N-acetylcysteine can prevent the nephrotoxic effect of ifosfamide on kidneys. Given the safe pharmacoprofile of N-acetylcysteine, its concurrent use with ifosfamide is recommended in patients who are going to receive ifosfamide. Other preventive measures such as urinary acidification requires further investigation.

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