



Case report

Sodium thiosulfate for postoperative cisplatin induced nephrotoxicity following hyperthermic intraperitoneal chemotherapy: A case report

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1. Introduction

The highly cytotoxic effect of cisplatin has led to its widespread utility as an anti-neoplastic agent for ovarian and many other types of cancers. Use of cisplatin is limited by well characterized side effects including neurotoxicity, myelosuppression, peripheral neuropathy and nephrotoxicity. For advanced ovarian cancer, cisplatin may be administered using hyperthermic intraperitoneal chemotherapy (HIPEC). This administration route allows direct and local delivery of chemotherapy to malignant cells with reduced systemic absorption (Armstrong et al., 2006; Van Driel et al., 2018). However, patients receiving intraperitoneal cisplatin still experience systemic side effects. Cisplatin is primarily cleared through the kidney thus nephrotoxicity and associated electrolyte disturbances are the most common side effects, reported at rates ranging from 1% to 5% of HIPEC administrations (Van Driel et al., 2018). Given the potential severity of cisplatin induced toxicities, many classes of protective agents have been used and investigated (Goel et al., 1989; Markowiak et al., 2019). Previous research has largely focused on concomitant administration of protective agents and chemotherapy (Dickey et al., 2005). While the onset of acute kidney injury (AKI) can be immediate, these effects can be durable. Less is known about the efficacy and utility of the renal protective agents when administered days after chemotherapy infusion. We present this case of management of cisplatin nephrotoxicity following HIPEC with delayed treatment with sodium thiosulfate (STS). This case suggests a new utility for this agent in rescue of severe cisplatin nephrotoxicity remote from infusion.

2. Case report

A fifty-two year old female with an advanced stage high grade mullerian adenocarcinoma presented from her medical oncologist for consideration of interval debulking surgery. Her history was notable for class III obesity (BMI 44), hypertension, type II diabetes mellitus, mild intermittent asthma, obstructive sleep apnea, bilateral pulmonary emboli, stage III chronic kidney disease, and history of prior right salpingo-oophorectomy for an endometrioma. The patient's baseline creatinine was 1.2 mg/dL and glomerular filtration rate (GFR) was 50 mL/min.

She was initially diagnosed with a 34 × 24 × 33 cm partially necrotic pelvic mass and bilateral segmental and subsegmental pulmonary emboli. A biopsy revealed a high grade mullerian carcinoma. The patient received 6 cycles of neoadjuvant chemotherapy with carboplatin (AUC 6) and paclitaxel (175 mg/m²), with reduction in size of the dominant mass to 30 cm in largest dimension. Given a partial response to neoadjuvant chemotherapy, decision was made to proceed with an interval debulking and HIPEC. She underwent exploratory laparotomy, adhesiolysis, left salpingo-oophorectomy, upper vaginectomy, bilateral ureterolysis, supracolic omentectomy, optimal interval tumor debulking to no gross residual disease, ventral umbilical hernia repair, and HIPEC with cisplatin (100 mg/m²). Approximately 60 min prior to infusion of cisplatin intraperitoneally, the patient received 30 g of mannitol 20% intravenous solution over 1 h as well as 40 mg of furosemide intravenously. Intraoperatively, urine output was maintained above 100 mL per

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hour. The patient's estimated blood loss was 700 mL and the patient was received 2 units of packed red blood cells (hemoglobin of 7.7 g/dL), 3 L of crystalloid, and 2 L of albumin

On arrival to the postoperative care unit, the patient was found to be hypotensive, with blood pressure of 88/54 mmHg, heart rate of 103 BPM, and temperature of 98.2°F. A repeat complete blood count (CBC) and complete metabolic profile (CMP) were obtained and the patient was admitted to the intensive care unit for resuscitation and close monitoring. Upon admission to the ICU, creatinine was elevated to 1.33 mg/dL, GFR of 42 mL/min, and hemoglobin was notably decreased to 6.5 g/dL. Her urine output was 160 mL per hour. She received 2 units of packed red blood cells and intravenous fluids were maintained at 30 mL/h. She was also started on a heparin drip for her history of bilateral pulmonary emboli.

On postoperative day 2, the patient's vital signs improved, with blood pressure of 118/50 mmHg, heart rate of 87 BPM and respiratory rate of 18. Her total urine output was stable at 100 mL per hour and she was transferred to the standard postoperative floor. Although her hemoglobin and blood pressure remained normal, her creatinine continued to increase. At this time, she had met all other post-operative milestones including toleration of an oral diet, ambulation, and her pain was controlled. A fractional excretion of urea was obtained at that time and was consistent with intrinsic renal disease and differential diagnosis pointed to likely acute tubular necrosis due to acute hypotension post-operatively. Between post-operative days 3–4, her creatinine continued to increase up to 2.07 mg/dL and GFR reduced to 25 mL/min. Urine output remained normal. A renal ultrasound of the kidneys revealed no evidence of hydronephrosis and a manual urinalysis revealed absence of muddy brown casts. The patient's creatinine continued to uptrend to 4.06 mg/dL and GFR decreased to 12 mL/min.

As her creatinine continued to increase and her repeat urinalysis was not consistent with acute tubular necrosis, cisplatin induced nephrotoxicity seemed to be the most likely etiology for her kidney injury. On postoperative day 7, the decision was made to administer sodium thiosulfate (STS) at 12 g/m² over 6 h. On postoperative day 9 the creatinine increased to 4.4 g/dL. Thereafter, the patient's creatinine began to decrease steadily until the day of discharge, on postoperative day 12, at which time the creatinine was 3.24 mg/dL and the GFR had improved to 15 mL/min. The patient continued to follow-up for weekly serum chemistries as an outpatient and creatinine and GFR continued to improve. As of her last follow-up, 6 weeks after surgery, the patient's creatinine had returned to near baseline.

3. Discussion

Interval cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin has been shown to improve overall survival in advanced ovarian cancer patients as compared to surgical cytoreduction alone (Van Driel et al., 2018). The implementation of HIPEC programs is expanding at various institutions around the world, and thus the potential adverse effects are important to understand. In particular, cisplatin associated acute kidney injury is not uncommon, but can be mitigated (Chambers et al., 2020). Management concerning cisplatin renal failure in the literature is minimal.

HIPEC has a high risk of nephrotoxicity secondary to hypotension due to venous capacitance (Rotruck et al., 2014). Additionally, cisplatin induced nephrotoxicity is a commonly known side effect when administered intravenously, but can be aggravated in patients undergoing HIPEC.

Cisplatin administered via intraperitoneal route will remain in the bloodstream for approximately 5 days (Miller et al., 2010). As cisplatin accumulates in the kidneys, nephrotoxicity can occur several days following administration. Previous research demonstrates the benefit of sodium thiosulfate (STS) administration in patients receiving HIPEC for ovarian cancer (Miller et al., 2010). These benefits include a decrease in cisplatin induced nephrotoxicity and an increase in the dosage of

cisplatin that could be given during HIPEC infusion. STS can bind and inactivate cisplatin in the kidneys to prevent cisplatin provoked and DNA damage mediated cell death (Laplace et al., 2020). More importantly, it can alleviate the cisplatin mediated damage to the mitochondria. Some studies indicate that STS concentrating in the kidneys can elevate to rapidly inactivate cisplatin (Miller et al., 2010).

STS has traditionally been administered either prior to or concomitantly with administration of cisplatin (Van Driel et al., 2018; Laplace et al., 2020). Other mitigation strategies for prevention of acute kidney injury include adequate hydration, furosemide and mannitol infusion during HIPEC to ensure adequate excretion and diuresis of cisplatin (Dickey et al., 2005). Currently there is no standard post-operative management of patients with cisplatin induced renal failure. Erdlenbruch et al. describe a case of a 14 year old pediatric patient who experienced ototoxicity and renal failure secondary to cisplatin overdose (Erdlenbruch et al., 2002). She was given a chemoprotective infusion of STS 6 days after the finding of the overdose. Urinary platinum excretion levels began to decrease following this infusion. This is similar to our case, where we saw a concomitant improvement in renal function as well as expanded diuresis.

This case demonstrates that, in the absence pre-renal and obstructive causes of AKI, STS can be used for cisplatin induced nephrotoxicity. Our case, which is the latest use of STS chemoprotection in the literature to our knowledge, shows that this mitigation strategy can be used many days after intraperitoneal cisplatin perfusion. While further studies are required to assess the timing with which STS is still effective in reducing cisplatin nephrotoxicity, our case does demonstrate its use as a rescue strategy to improve nephrotoxicity.

CRedit authorship contribution statement

K. Patel: Investigation, Writing - original draft, Writing - review & editing. **A. Asare:** Investigation, Writing - original draft, Writing - review & editing. **S. Moufarrj:** Investigation, Writing - original draft, Writing - review & editing. **A.B. Costales:** Investigation, Writing - original draft, Writing - review & editing, Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Armstrong, D.K., Bundy, B., Wenzel, L., et al., 2006. Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer. *New Engl. J. Med.* 354, 34–43.
- Chambers, L.M., Costales, A.B., Crean-Tate, K., et al., 2020. A guide to establishing a hyperthermic intraperitoneal chemotherapy program in gynecologic oncology. *Gynecol. Oncol.* 158 (3), 794–802.
- Dickey, D.T., Wu, Y.J., Muldoon, L.L., Neuwelt, E.A., 2005. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. *J. Pharmacol. Exp. Ther.* 314 (3), 1052–1058.
- Erdlenbruch, B., Pekrun, A., Schiffman, H., et al., 2002. Accidental cisplatin overdose in a child: reversal of acute renal failure with sodium thiosulfate. *Med. Pediatr. Oncol.* 38, 349–352.
- Goel, R., Cleary, S.M., Horton, C., et al., 1989. Effect of sodium thiosulfate on the pharmacokinetics and toxicity of cisplatin. *J. Natl Cancer Inst.* 81 (20), 1552–1560.
- Laplace, N., Kepenekian, V., Friggeri, A., et al., 2020. Sodium Thiosulfate Protects from Renal Impairment Following Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Cisplatin. *Int. J. Hyperth.* 37 (1), 897–902.
- Markowiak, T., Kerner, N., Neu, R., et al., 2019. Adequate nephroprotection reduces renal complications after hyperthermic intrathoracic chemotherapy. *J. Surg. Oncol.* 120 (7), 1220–1226.
- Miller, R.P., Tadagavadi, R.K., Ramesh, G., et al., 2010. Mechanisms of Cisplatin Nephrotoxicity. *Toxins* 2 (11), 2490–2518.
- Rotruck, S., Wilson, J.T., McGuire, J., 2014. Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy: a Case Report. *AANA J.* 82 (2), 140–143.
- Van Driel, W.J., Koole, S.N., Sikorska, K., et al., 2018. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *New Engl. J. Med.* 378, 230–240.