

Case Report

Hepatic necrosis and hemorrhage following hyperthermic intraperitoneal chemotherapy with oxaliplatin: A review of two cases

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Introduction

Cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is now becoming a standard of care for peritoneal carcinomatosis (PC) in selected patients. Eradication of macroscopic disease (nodules > 2.5 mm) is realized through meticulous CS. Following CS, intraperitoneal chemotherapy is administered to treat microscopic disease (1). An increasing number of patients presenting with PC arising from colorectal cancer (2,3), pseudomyxoma peritonei (4), and malignant peritoneal mesothelioma (5) have been treated using this combined modality with promising results. However, this procedure is associated with significant morbidity. Major complication rates reach 52% in some series (6). Sepsis, abscesses, anastomotic leaks, thromboembolic events, haematological toxicity and renal insufficiency are the main complications described in literature (6). We herein report two unusual cases of hemorrhagic shock with hemoperitoneum associated with severe hepatic necrosis following CS and HIPEC with oxaliplatin (HIPEC-OX).

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Over 75 HIPEC-OX have been performed in the past five years in our center. HIPEC is performed with the abdomen open using the Coliseum technique, with skin edges retracted above the surface of the abdomen on a metallic ring. Chemotherapy solution (oxaliplatin 460mg/m² diluted in a 2L/m² volume of D5%W) is delivered in a continuous closed circuit using four 36-French drains (two inlets and two outlets) connected to two pumps. The flow rate is 1L/min for each pump, and four thermal probes inside the peritoneal cavity give continuous temperature feedback. Intra-abdominal temperature is maintained between 42°C and 44°C and the perfusion duration is 30 minutes. The infusion is then completely evacuated and the abdomen is closed. In our institution, intraperitoneal chemotherapy is not associated with simultaneous intravenous chemotherapy (5-fluorouracile), except for patients with colorectal PC.

Various chemotherapeutic agents have been proposed for HIPEC (7). Oxaliplatin, a third generation platinum complex derived from cisplatin, is a commonly used agent and one of the preferred agent for PC arising from colorectal carcinoma. It has proven activity against colorectal cancer cells and has high intra-tumoral penetration and intra-peritoneal concentration. Moreover, oxaliplatin's cytotoxicity is potentiated by hyperthermia and has a low systemic absorption, with possibly less systemic toxicity (8,9).

Case Report

A 46 year-old woman was diagnosed with a left ovarian mucinous cystadenoma in 1996. She underwent a left

salpingo-oophorectomy and appendectomy. Her medical history was otherwise unremarkable, with no history of coagulopathy. Follow-up was uneventful until she developed ascites in 2004. A diagnostic laparoscopy showed diffuse pseudomyxoma peritonei. The patient was transferred to our institution for preoperative evaluation and treatment. In November 2005, the patient underwent complete surgical cytoreduction, including multiple peritonectomies, total omentectomy and right hemicolectomy. Her peritoneal carcinomatosis index (PCI) score [1], reflecting the extent of PC, was 15. HIPEC-OX was then administered. No complication occurred during surgery, blood loss was minimal and the patient returned to the ward after the intervention. On postoperative day one, the patient developed sensory neuropathy involving her distal upper and lower limbs that were attributed to oxaliplatin neurotoxicity. Three days later, the patient developed a severe hemorrhagic shock and hepatic failure. The hemoglobin level decreased to 52 g/L and transaminase liver enzymes raised to 6600. She was emergently brought back to the operating room, where damage control surgery with abdominal packing and lavage were performed. Multiple hepatic lacerations with massive bleeding were noticed. On day one after her second surgery, she suffered cardiac arrest for which she received aggressive reanimation. In the post-operative course, the patient developed disseminated intravascular coagulation followed by severe renal insufficiency requiring continuous veno-venous hemofiltration. She also had an infected hepatic necrosis with severe liver failure (total bilirubin count of 800 $\mu\text{mol/L}$), which was supported with albumin dialysis. Three other surgeries were needed for debridement of the necrotic liver and lavage of the peritoneal cavity. Her condition slowly improved afterwards and she was discharged from the hospital on day 97. At follow-up visits, she had regained her renal and hepatic functions. She was finally reoperated for incisional hernia repair and the postoperative course was uneventful. She is currently disease-free.

The second patient is a 37 year-old man of Mexican origin with an unremarkable past medical history. He had no history of asbestos exposure or any coagulopathy. In April 2006, he presented with diffuse abdominal pain and distension. Abdominal ultrasound showed an important mass in the left inferior quadrant and a diagnosis of epithelioid mesothelioma was confirmed by percutaneous biopsy. The patient was initially treated with systemic chemotherapy (cisplatin and gemcitabine) with some response. In October 2006, the patient suffered a thrombotic stroke attributed to gemcitabine. Chemotherapy was stopped and the patient was treated with low molecular weight heparin as well as anticonvulsant therapy for residual

seizures. He completely recovered from this episode. Two months later, he underwent an incomplete cytoreduction of his mesothelioma (omentectomy and appendectomy) in Mexico. The post-operative course was uneventful. Few weeks later, he consulted our team for an opinion regarding treatment of his residual disease. At preoperative workup, the disease seemed to be resectable and hepatic and coagulation functions were completely normal. Cytoreductive surgery including left hemicolectomy, splenectomy, gastric wedge excision, and diverting loop ileostomy were performed in June 2007. The PCI score was 13. HIPEC-OX was then performed as previously described. Surgery was uneventful, and total blood losses were estimated at 500 ml. On postoperative day one, the patient developed hypotension with a hemoglobin count of 68 g/L. Fresh blood was emerging from the abdominal wound. He was transferred to the operating room, where an important hepatic laceration at the inferior border of segment V with ongoing bleeding was noticed. Hemostasis and damage control surgery were performed with extensive packing to control hemorrhage. The following day, the patient returned to the operating room for removal of packing material. At surgery, bleeding was under control but the gallbladder appeared necrotic. Cholecystectomy was performed and the V.A.C.[®] abdominal dressing system was used to close the abdomen. He later developed hepatic dysfunction with liver enzymes up to 5300 and alkaline phosphatase at 340. Coagulation values were mildly elevated. Five other abdominal explorations and V.A.C.[®] dressing changes were necessary. Twenty days following CS, he underwent a partial right hepatectomy for excision of infected hepatic necrosis. He slowly regained his hepatic function and his sepsis was successfully treated with antibiotics. He was discharged after 66 days of hospitalisation. He was later reoperated to repair his large ventral hernia and he recovered very well. He finally presented a recurrence of peritoneal mesothelioma in November 2010.

Discussion

To our knowledge, severe hemorrhagic shock combined with hepatic insufficiency and necrosis following HIPEC-OX has not been reported. Histopathologic analysis of necrotic hepatic tissues did not reveal the cause of injury. Hepatic parenchyma was difficult to identify and specimens were mostly composed of blood clots and devitalized necrotic tissues. Local or systemic oxaliplatin toxicity and direct thermal injury to the liver could possibly be responsible for this unusual complication.

Oxaliplatin is a platinum-derived alkylating agent. Following intracellular hydrolysis, the platinum compound

binds to DNA, forming cross-links that inhibit DNA replication and transcription, resulting in cell death. Its cytotoxic activity is cell-cycle independent (10). Frequently encountered side effects following systemic administration include emesis, diarrhoea, mild to moderate myelosuppression (neutropenia, thrombocytopenia), as well as peripheral neuropathy. Asthenia, anemia, fever, skin rash and laryngospasm may also be observed (11). Rarely, severe hypersensitivity reaction associated with thrombocytopenia can occur (12). Mild elevation of liver enzymes has also been reported (11). However no clinically significant hepatic insufficiency or necrosis has been reported.

In studies using HIPEC-OX, high doses of oxaliplatin are used (460mg/m² compared to 85-100 mg/m² for systemic treatment). Unexplained postoperative hemoperitoneum episodes have been observed (8,13). However, only mild haematological and hepatic toxicity (transient elevation of transaminases) have been reported, without clinically significant bone marrow depletion or liver insufficiency (13). Very rarely do the previously mentioned toxicity related to systemic treatment occur during HIPEC because the cytotoxic agent exerts its action mainly loco-regionally, with little systemic absorption (8,14).

Nevertheless, oxaliplatin may be responsible for the severe complications described in our two cases. The mechanism by which this toxicity exerted its effects remains to be elucidated. In the two cases, the liver was initially relatively spared by the disease. The tumor nodules on the liver were destroyed by electrofulguration, and therefore the Glisson's capsule was not entirely removed, but left in place with breaches. Since we have performed several HIPEC-OX after complete removal of Glisson's capsule without hepatic necrosis, we hypothesize that when leaving most of Glisson's capsule intact but with small breaches due to electrofulguration, some entrapment of oxaliplatin could occur under the capsule and result in high local toxicity. Small unrecognized hepatic lacerations from cytoreduction, tube placement or even thermic injury, may serve as a site for oxaliplatin entrapment with subsequent bleeding, excessive local toxicity, hepatic cell death and necrosis.

Alternatively, oxaliplatin may have induced toxicity through a systemic route. It is possible that increased systemic absorption of high dose of oxaliplatin may have induced severe liver dysfunction. This is particularly true for our first patient who developed neuropathy (a known effect of oxaliplatin systemic overdose). Chemo-induced vasculitis was also suspected, but was not confirmed. An atypical hypersensitivity reaction could also finally explain this rare complication.

Technical contributing factors may also be involved. In HIPEC, hyperthermia mainly serves to exert direct physical

stress on tumor cells and, more importantly, potentiate the cytotoxic effects of chemotherapy. The cytotoxicity of oxaliplatin is increased by 180% when heated at 43°C. We applied a plateau temperature of 42°C for all of our HIPEC procedures without evidence of thermal injury. It is however possible that hepatic thermal injury was induced by a misplaced heat generator with resulting hepatic necrosis secondary to heat. One must also consider that the necrosis observed was exacerbated by infectious agents. Intraoperative technical difficulties could have lead to parenchymal laceration, vascular trauma and bleeding. However, there was no evidence of vascular trauma in both surgeries. Furthermore, we did not administer any vascular endothelial growth factor (VEGF) inhibitor to these two patients before surgery, which could have explained increased perioperative morbidity.

In conclusion, hepatic necrosis is an unusual complication of HIPEC. Oxaliplatin entrapment within Glisson's capsule or within hepatic lacerations could induce local or systemic toxicity with resultant parenchyma necrosis. Thermal injury may be contributory, and therefore extreme caution should be exerted to avoid it.

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