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Hyperthermic intraperitoneal chemotherapy with cisplatin: Amifostine prevents acute severe renal impairment

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Abstract

Surgical cytoreduction combined with intraperitoneal chemo-hyperthermia (HIPEC) has shown to provide survival benefits in the management of some peritoneal carcinomatosis. The cisplatin (CP) used in HIPEC carries a risk of renal impairment (RI). This risk could be reduced by administration of amifostine (A). The aim of our study was to assess the utility of A in preventing RI during IPCH with CP.
Patients and methods: Retrospective study including patients who underwent HIPEC between January 2007 and June 2013. The HIPEC involved administration of CP and mitomycin C, between 41 and 43 °C. The peri-anaesthetic management was consistent to use A after 2010. Renal function was assessed from the measured creatinine clearance (CreatCl) and the change between D0 and D4 was compared between patients who received A (group A+) and those who did not (group A−). Severe RI was defined as the development of a CreatCl of <30 ml/min. The statistical analysis used a Student t-test and Fischer's exact test. A p-value of <0.05 was deemed to be statistically significant.
Results: Over the studied period, seventy five patients underwent HIPEC and the findings from fifty two patients were analysed: thirty one in group A+ and twenty one in group A−. The change in mean CreatCl from D0 to D4 did not differ between the two groups although between D1 and D4 a significantly higher percentage of severe RI was seen in group A−.
Conclusions: This study has shown A to offer benefit in terms of reducing severe RI when CP is used in HIPEC. These results, however, will need to be confirmed in prospective series on larger numbers of patients.

Keywords: Hyperthermic intraperitoneal chemotherapy; Cisplatin; Amifostine; Renal impairment

Introduction

Peritoneal carcinomatosis has long been considered to be the end stage of cancer with death in the short term. Since the 1990s the introduction of management combining peritonectomy procedures with intraperitoneal chemo-hyperthermy (HIPEC) has shifted a palliative approach to a curative one.[1] This strategy has been shown to be beneficial in carefully selected patients.[2–4] The main indications for this treatment are still peritoneal carcinomatosis secondary to colorectal, ovarian and gastric cancers and primary peritoneal tumours (pseudomyxoma and peritoneal mesothelioma). In this approach, the macroscopic disease is treated by careful total surgical resection and the residual microscopic disease is treated with HIPEC. The intraperitoneal chemotherapy under hyperthermic conditions, between 41 °C and 43 °C, has a synergistic effect with antimitotic therapy[5,6] and minimise the exposure of healthy tissues.[7] Cisplatin (CP) and mitomycin C are the most widely used

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anti-cancer drugs in HIPEC. Whilst mitomycin C, however, has bone marrow toxicity,[8] CP is known to be directly nephrotoxic, with a risk of renal impairment (RI) including when it is used in the context of HIPEC.[9,10] This risk may be reduced by administrating amifostine (Ethyol®) (A).[11] This agent is believed to improve renal CP tolerance. The suggested mechanisms of action are binding free radicals, transfer of hydrogen to DNA groups, depletion of oxygen close to DNA and an increase in the biochemical DNA repair mechanisms.[11] A, however, has side effects and is responsible for occasionally severe hypotension which may worsen the haemodynamic stability seen in HIPEC.[12] Major changes in volume occur during HIPEC: from the cytoreduction phase onwards, large amounts of fluid are lost from the wide incision, possible removal of ascites, extensive resection of the peritoneal surface area and the duration of cytoreduction. Secondly, musculocutaneous vasodilatation secondary to the hyperthermia with splanchnic vasodilatation, contributes to these changes in volume.[13] In this background, the benefit risk balance of A to prevent RI remains debated. The aim of our study was to assess the utility of A in preventing RI during HIPEC with CP.

Patients and methods

Study population and surgical technique

We retrospectively recorded anonymised data on patients treated with cytoreduction and HIPEC between January 2007 and June 2013 in the Louis Mourier university hospital centre (Colombes, Paris Hospitals Health Service). The study was approved by the ethics committee and the data collected included age, sex, weight, height, body mass index (BMI), American Society of Anaesthesiologists (ASA) class, the primary tumour responsible for the carcinomatosis, the use of peridural analgesia, duration of the procedure, duration of anaesthesia, dose of CP and A, estimated insensible skin losses based on a rate of 6–8 ml/kg per hour, the number of patients who required transfusion with blood and/or fresh frozen plasma (FFP) perioperatively, the number of bags of packed red blood cells (PBC) transfused and bags of FFP administered, the volume of crystalloids and colloids infused perioperatively, use of vasopressor agents and the dose administered, creatinine clearance measured preoperatively and postoperatively from D1 to D4 and the need for renal replacement therapy. The surgical technique has been described in detail elsewhere.[14] After complete tumour cytoreduction combined with peritonectomy, open perioperative HIPEC was started with a peritoneal suspension. Drains were positioned within the abdomen in order to irrigate the peritoneal cavity with the chemotherapy solution which consisted of 3 L of physiological saline containing 75 mg/m^2 of CP and 20 mg/m^2 of mitomycin C. A ten minute preheating phase was used with a heating pump to reach an average temperature of 42 °C. Irrigation of the abdominal cavity was then started and continued for a period of thirty minutes. Intra-abdominal temperature was monitored continuously with a thermal probe in order to meet the desired temperature of 42 °C throughout the entire procedure. The entry and output temperatures of the liquid were also monitored continuously as was oesophageal temperature.

Anaesthetic and postoperative management

The peri-anaesthetic management was consistent over the studied period and followed a local procedure which was not changed apart from the non-routine use of A from 2010 onwards. In the group which received A (A+), the A (910 mg/m^2) was administered over fifteen min, thirty minutes before starting the HIPEC with CP. In group A−, the patients were not given A. All patients underwent an anaesthesia consultation at least forty eight hours before surgery and were hospitalised on the day before the procedure in the department of gastrointestinal surgery. They began fasting at midnight. On the morning of the procedure they were all given anxiolytic premedication. Prior to induction anaesthesia, a thoracic peridural access was established for postoperative analgesia whenever possible, if not contraindicated. The anaesthesia was then started by an intravenous induction with propofol, sufentanil or remifentanil and atracurium, and patients underwent oral tracheal intubation. General anaesthesia was continued with desflurane or sevoflurane, sufentanil or remifentanil and atracurium throughout the whole procedure. Generous vascular filling was given, possibly combined with administration of catecholamines guided by the haemodynamic monitoring. Patient observation and monitoring during anaesthesia were adapted to the type of surgery and the patient's background: conventional haemodynamic monitoring was supplemented with invasive arterial blood pressure measurement and blood volume monitoring (Vigileo® oesophageal Doppler ultrasound) as assessed by the practitioner looking after the patients: monitoring of depth of anaesthesia from the bispectral index and central temperature monitoring with an oesophageal probe. Following surgery, the patients were transferred to the postoperative recovery room (PORR) in a continuing surveillance unit (CSU) or intensive care, depending on their clinical state. Postoperatively, patients were given peridural anaesthesia with ropivacaine 0.2% and morphine 0.025% in PCEA mode. If a peridural line was not present, IV morphine PCEA was started. In addition, multimodal analgesia with paracetamol (1 g × 4/24 h), ketoprofen (50 mg × 4/24 h for 48 h) and nefopam (80 mg by push syringe every 24 h)

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