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Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with primary and recurrent advanced ovarian cancer

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Abstract

Background: The aim of this study is to report the perioperative outcomes of CRS and HIPEC from a single institution and review those factors that are associated with a poor perioperative outcome in patients with peritoneal dissemination from primary or recurrent ovarian cancer.

Patients and method: A retrospective cohort study setting was conducted in a third level hospital peritoneal surface malignancy program. Ninety one patients diagnosed with ovarian peritoneal carcinomatosis, primary and recurrent without extraperitoneal metastasis were included for cytoreductive surgery and HIPEC with paclitaxel. We analyzed the postoperative morbidity rates and a univariate and multivariate analysis of factors associated with overall (grade I–IV) and major (grade III–IV) postoperative morbidity were performed.

Results: Peritoneal Cancer Index (PCI) upper than 12 (OR = 2.942 95%: 1.892–9.594 $p = 0.044$) was an independent factor associated with the occurrence of I–IV postoperative morbidity. Regarding major complications (grade III–IV), on multivariate analysis, in addition to PCI >12 (OR = 6.692, 95% CI: 1974–45, 674, $p = 0.032$), the need to carry out intestinal resection (OR = 4.987, 95% CI: 1350–27, 620, $p = 0.046$) was an independent factor related with major morbidity (grade III–IV).

Conclusions: The use of HIPEC after aggressive cytoreductive surgery in patients with ovarian cancer with peritoneal dissemination can be performed with acceptable postoperative morbidity rates. Knowledge of the factors associated with the onset of these postoperative adverse events allows better management of the same and offers the patient a safe procedure.

Keywords: Ovarian cancer; Morbidity; Cytoreductive surgery; HIPEC

Introduction

The use of chemotherapy hyperthermic intraoperative intraperitoneal (HIPEC) subsequent to the completion of extensive surgical debulking procedures has generated survival rates above 90% at 5 years in patients with pseudomyxoma peritonei[1] and above 60% in patients with peritoneal mesothelioma.[2] In patients with colon cancer and peritoneal carcinomatosis (PC), Verwaal et al.,[3] published the only prospective randomised study that currently exists on the treatment of PC of colorectal origin by peritonectomy procedures and HIPEC administration in 2003. The study showed an improvement in both disease-free survival and overall survival for patients treated with HIPEC, compared with the conventional group, which only administered systemic chemotherapy. In advanced ovarian carcinoma, there is currently no prospective, randomised study that has demonstrated that the administration of HIPEC following cytoreductive surgery (CRS) exceeds cytoreduction alone, and papers published to date provide a great heterogeneity in patients as well as in the scheme used during HIPEC. However, the results are encouraging, with over 60% survival at 5 years follow-up.[4]

The morbidity rate after maximum effort cytoreduction and HIPEC administration in ovarian carcinoma ranges from 15 to 45%, with a procedure-related mortality of 0–10%.[5] The study of the morbidity and mortality associated with maximum effort cytoreduction and HIPEC application allows the identification of the risks of this

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therapeutic procedure in patients with peritoneal dissemination of ovarian cancer until the expected results of prospective randomized trials ongoing.[6]

The aim of this study is to report the perioperative outcomes of CRS and HIPEC from a single institution and review those factors that are associated with a poor perioperative outcome in patients with peritoneal dissemination from primary or recurrent ovarian cancer.

Patients and methods

Selection of patients

In the present study, we included 91 consecutive patients diagnosed with ovarian peritoneal carcinomatosis from January 2008 to July 2011, both primary and recurrent. The inclusion criteria were as follows: ages between 18 and 80 years, adequate baseline performance status (ECOG 0-1), patients with primary ovarian carcinoma stage IIIB–C or IV (provided that the neoadjuvant chemotherapy has succeeded in limiting the disease to the peritoneal cavity), and in patients with recurrent disease, those with a disease-free interval of at least 6 months after completion of systemic chemotherapy (platinum-sensitive recurrent ovarian cancer).

Every patient had adequate cardiac, renal, hepatic and bone marrow function, and rigorous patient selection was performed using American Society of Anesthesiologist (ASA) score (http://www.asahq.org/clinical/physicalstatus.htm). Patients with ASA IV were not considered for CRS and HIPEC.

Surgical protocol

The staging of the degree of tumour extension was performed with the peritoneal carcinomatosis index (PCI) described by Sugarbaker,[7] establishing a value between 1 and 39. Every patient followed the same routine, beginning with surgery in the pelvic region, practicing pelviperitonectomy including the uterus, adnexal tissue (if they had not previously been removed), and the peritoneum of the Douglas pouch. If the rectosigmoid region was affected, it was resected "en bloc" with digestive reconstruction by mechanical colorectal anastomosis. The use of a protective ostomy of colorectal anastomosis was restricted to patients with an affected rectosigmoid region submitted to anastomosis of the lower third of the rectum. Cytoreduction was then completed in the rest of the peritoneal cavity, systematically practicing full supramesocolic omentectomy and an appendectomy, if they had not been done previously. The paraaortic and pelvic lymphadenectomy was reserved for those patients with macroscopic nodal disease preoperatively suspected on CT scan, or in those patients in whom presence of tumour was confirmed by intra-operative frozen section. Resection of the ureter or bladder was contemplated in those cases where, in addition, it was possible to achieve an optimal cytoreduction. The result of cytoreduction was classified according to "Cytoreductive Completeness Score" (CCS).[7]

Hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC)

Cytostatic paclitaxel was used at doses of 60 mg/m^2 of body surface area. The use of cisplatin, with doses of 75 mg/m^2 of body surface area was contemplated in those patients with previous hypersensitivity reactions to taxanes (paclitaxel and/or docetaxel). The cytostatic agent was diluted in 3 L of 1.5% dextrose solution for peritoneal dialysis, and infused maintaining a constant flow of 0.5–0.7 L/minute during 60 min. Two intra-abdominal thermometers (positioned in the pelvis and in the diaphragm area) were used to monitor the temperature inside the peritoneal cavity during the infusion, which remained constant, between 42 and 43 °C, for a total of 60 min.

Postoperative morbidity

Adverse events were classified according to the common toxicity criteria of the National Cancer Institute (NCI-CTC version 3.0).[8] Adverse events were graded 0–V in accordance with the National Cancer Institute's Common Toxicity Criteria. Mild complications required medical or no treatment for resolution (grade I/II). Moderate complications required interventional procedures for resolution, such as a CT or ultrasound-guided percutaneous drainage (grade III). Severe complications required returning to the operating room or intensive care support (grade IV). Perioperative death was defined as patient's death within 30 days of surgery or during the hospital admission (grade V).

Paralytic ileus was considered as a mild complication (grade I–II) and defined as the presence of abdominal distension, nausea and vomiting in the postoperative period. The positioning of a nasogastric tube was considered when conservative measures failed (digestive rest, intravenous therapy and metoclopramide administration). The occurrence of postoperative pleural effusion was considered to be an adverse event in those patients who required the positioning of a pleural drainage tube (voluminous pleural effusion or the appearance of accompanying respiratory symptoms).

Statistical analysis

The data was included in a prospective database established at the beginning of the surgery program at our peritoneal carcinomatosis centre and was analysed with the Windows SPSS v.1.70 program (Chicago, Illinois, USA). We first performed a descriptive statistical analysis for each of the variables, and considered continuous variables using the median and mean ± standard deviation. For qualitative variables we used frequencies and percentages.