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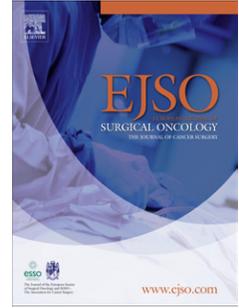
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**PERIOPERATIVE FAST TRACK PROGRAM IN
INTRAOPERATIVE HYPERTHERMIC INTRAPERITONEAL
CHEMOTHERAPY (HIPEC) AFTER CYTOREDUCTIVE SURGERY
IN ADVANCED OVARIAN CANCER.**

**Pedro Antonio Cascales Campos*, José Gil Martínez*, Pedro J. Galindo Fernandez*,
Elena Gil Gomez*, Isabel María Martínez Frutos*, Pascual Parrilla Paricio***

***Department of Surgery.**

Virgen de la Arrixaca University Hospital (Murcia-Spain)

Contact Author

Pedro Antonio Cascales Campos

Calle Dr Fleming N° 12 3° E

La Alberca, Murcia (Spain)

CP: 30150

e-mail: cascalex@yahoo.es

ABSTRACT

INTRODUCTION: Diffuse peritoneal dissemination in advanced ovarian cancer can be treated using optimal effort surgery involving peritonectomy procedures and the administration of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC).

OBJECTIVE: To report on our experience in the treatment of advanced ovarian cancer using peritonectomy procedures and HIPEC through the fast track program.

PATIENTS AND METHOD: From September 2008 until May 2010, forty-six patients with primary advanced (stage III-C) or recurrent ovarian cancer have been included in the fast track protocol if they had optimal cytoreduction CC-0 or CC-1 accompanied by HIPEC and there had no more than one digestive anastomosis.

RESULTS: The mean peritoneal cancer index (PCI) was 12.35 (3-21). The median operation time was 380 minutes (200-540). Optimal surgery CC-0 was achieved in 38 of the 46 patients and CC-1 in the remaining 8. Mean postoperative hospital stay was 6.94 ± 1.56 days (3-11). Major morbidity rates were 15.3%. Paralytic ileus was the most frequent of these. There was no mortality related to the procedure.

CONCLUSION: Surgery with peritonectomy procedures and HIPEC in advanced ovarian carcinoma is possible under fast track surgery programs in patients with low volume peritoneal carcinomatosis. Prospective and randomized studies are needed.

INTRODUCTION

Since Sugarbaker's publication in 1995 about the surgical treatment of peritoneal carcinomatosis (1), the approach for the peritoneal dissemination of pathologies such as colorectal carcinoma, peritoneal pseudomixoma, peritoneal mesotelioma and advanced ovarian carcinoma has undergone serious remodelling. The approach changed from non-committal attitude toward the diagnosis of peritoneal carcinomatosis to a much more active attitude leading to more aggressive surgery being carried out including peritonectomy procedures and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) (2-21). The overall rate of severe perioperative morbidity ranged from 0 to 40% and the mortality rate varied from 0 to 10% (22-29), with a mean hospital stay of over two weeks (21, 23, 26, 31, 33). Among factors related to morbidity and mortality, the learning curve is a crucial factor (30).

Fast-track surgery is a comprehensive approach, designed to accelerate recovery, reduce morbidity and shorten convalescence to ultimately improve outcomes and reduce costs (32). The introduction of Fast-track programs achieves good results in postoperative outcomes in many surgical pathologies (34-41). For instance, nephrectomy (42); radical prostatectomy (43); knee and hip prosthesis (44); abdominal aortic aneurysm (36); bariatric surgery (45,46) and lung resections (47) can all be carried out with a mean hospital admittance of less than 4 days and others such as antireflux surgery; suprarenalectomy; cholecystectomy; thyroidectomy; etc, are already carried out in many hospitals in ambulatory care (48,49). In the literature no experience has been reported of fast-track programs in surgery with peritonectomy procedures and HIPEC for peritoneal surface malignancies such advanced ovarian cancer.

This study evaluated fast-track protocol in patients with advanced ovarian carcinoma who underwent peritonectomy procedures and HIPEC.

PATIENTS AND METHOD

From September 2008 until May 2010, 57 patients previously diagnosed with primary advanced (stage IIIC) or recurrent ovarian cancer have been treated using peritonectomy procedures and HIPEC. All patients have been informed about surgery together with recovery under the fast track protocol. We limited the protocol to patients who had optimal cytoreduction, HIPEC administration, and no more than one digestive anastomosis.

SURGICAL PROTOCOL

A xiphopubic laparotomy was performed, evaluating the overall resectability of the peritoneal disease. Stratification of the grade of extension into the abdominal cavity was carried out according to Sugarbaker's criteria (1), establishing the Peritoneal Cancer Index (PCI) which ranges from 1 to 39. Peritonectomy procedures were performed according to Sugarbaker's method. Surgery began in the pelvis, involving a pelvipertonectomy, including total hysterectomy and bilateral salpingoophorectomy if they had not been removed previously, as well as the Douglas pouch. If the rectosigma was affected, it was also resected as a block together with the other pelvic organs described. Afterwards, the cytoreduction of the rest of the cavity was continued by carrying out systematic omentectomy. If the spleen was affected, it was resected as a block together with the large omentum. In patients with affection of the right diaphragmatic peritoneum, prior to the peritonectomy, complete liver mobilisation was carried out. The resection of the small intestine was limited to those segments where a simple incision of the serosa was impossible. A colectomy with resection of the lesser omentum was carried out if they were affected, with special care taken not to cause a lesion to the left gastric artery. Pelvic and paraaortic lymphadenectomy was reserved for patients with lymph node disease visible in the preoperative CT scan, TAC-PET or when there was an intraoperative finding of suspected lymph node disease confirmed by intraoperative biopsy. Abdominal drainage was systematically left in the pelvis. We considered optimal CC-0 surgery when there was no macroscopic tumor residue at the end of cytoreduction and optimal CC-1 when there was less than 2.5 mm of tumour residue after cytoreduction according to Sugarbaker's Completeness Cytoreductive Score (CCS) (1). After optimal cytoreductive surgery, intraoperative perfusion of the peritoneal cavity with HIPEC was applied as described.

HYPERTHERMIC INTRAOPERATIVE CHEMOTHERAPY (HIPEC).

Our group uses a 60 miligrams/m² dose of the intraperitoneal cytostatic paclitaxel (32 patients) according with the excellent results reported previously by Rufian et al (19) and BAE et al (20). The use of a 75 miligrams/m² dose of cysplatin was indicated in 3 patients because during previous systemic chemotherapy they developed an allergy with anaphylactic reactions to paclitaxel and docetaxel. Cytostatic was diluted in 3 litres of 1.5% dextrose peritoneal dialysis solution. After cytoreduction the peritoneal cavity was positioned according to the “Coliseum” technique. In the perfusion circuit there was a constant flow of approximately 0.5-0.7 litres/minute during 60 minutes. Two intracavity thermometers monitored the temperature within the peritoneal cavity during perfusion, which was kept constant between 42-43 °C. An esophageal thermometer monitored the patient’s central temperature.

FAST-TRACK PROGRAM.

All patients received a low-residue diet one week before surgery and were admitted 1 day before surgery. No absolute diet was established on admittance. Sugary drinks were permitted until 3 hours before the intervention. We do not recommend systematic mechanic preparation of the colon. Preoperative venous thromboembolism prophylaxis with low weight molecular heparine was administered 12 hours earlier, as well as oral prophylaxis of the peptic disease with omeprazol (40 miligrams). Anesthetic management included the positioning of a low thoracic epidural catheter (T8-T10). Throughout the entire intervention there was strict monitoring of the temperature, maintaining a normothermic temperature (37°C), using physical measures and intravenous fluids therapy at different temperatures depending on the phase of surgery (warm during cytoreduction and cold during the HIPEC procedure). Empiric use of perioperative antibiotics was initiated at the time of operation and continued for a total of 72 hours postoperatively. After the intervention, a nasogastric tube was not used. Postoperative treatment included prokinetics (10-20 mgrs intravenous metoclopramide every 8 hours). Intravenous drip therapy was adjusted according to the PVC (desirable figures of 5-10 cms of H₂O). Early oral feeding was introduced in the first day. Pelvic drains were removed before discharge if not otherwise contraindicated. Criteria for hospital discharge included tolerance of regular diet and satisfactory pain control with oral agents alone.

MORBIDITY AND MORTALITY

Morbidity and mortality data were collected. Adverse events were graded I–IV in accordance with the National Cancer Institute’s common toxicity criteria. Mild complications required medical or no treatment for resolution (grade I/II respectively). Moderate complications required interventional procedures for resolution, such as a CT- or ultrasound-guided percutaneous drainage (grade III). Severe complications required a return to the operating room or intensive care support (grade IV). The presence of abdominal distension, nausea and vomiting was considered as a paralytic ileus. The nasogastric probe was only used if the patient did not improve after conservative treatment (gastrointestinal rest, fluid therapy and metoclopramide). Pleural drainage was considered as an adverse event in those cases in which the positioning of a pleural drainage tube was needed for its resolution (voluminous or appearance of respiratory symptoms).

RESULTS

Forty-six patients (80.7%) were enrolled and 11 patients were excluded from the protocol, (6 because they required at least 2 digestive anastomoses and 5 because they could not carry out optimal surgery for their peritoneal disease). Thirty-seven patients (80.4%) had received systemic chemotherapy before being treated in our unit with a mean number of 7.86 ± 5.63 preoperative chemotherapy cycles per patient (3-18 cycles per patient). The characteristics of the patients are shown in table 1. The median age was 57 years (38-78 years). PCI, surgical procedure, Completeness Cytoreductive Score (CCS), surgery time, ICU and hospital stay are shown in table 2. The average PCI index was 12.35 (3-21), with a median operation time of 380 minutes (200-540 minutes). After cytoreduction, optimal CC-0 surgery was achieved in 38 patients (82%) and CC-1 in the remaining 8. Cytoreductive surgery of the pelvis with peritonectomy procedures, as well as omentectomy was the most frequent surgical technique. There were 23 patients who underwent intestinal resection: small bowel resection (6 patients), right hemicolectomy (3 patients), and rectosigmoid (14 patients). Right diaphragmatic peritonectomy (8 patients), splenectomy (2 patients), ureter resection (1 patient) and left diaphragmatic peritonectomy (1 patient) were needed to achieve complete cytoreduction. Seventeen patients (42 %) were subjected to some kind of lymphadenectomy (complete retroperitoneal lymphadenectomy in 6 patients and pelvic lymphadenectomy in the remaining 11). 35 patients (76%) required a red blood transfusion with a median of 2 red blood cell units (0-5).

37 patients (80.4%) included in the protocol fulfilled the complete postoperative scheme. The overall grade I-II morbidity rate was 21%. A Grade III-IV morbidity rate was found in 7 patients (15.3%) (Table 3). Paralytic ileus (6 patients) was the most common complication. Only two patients with paralytic ileus needed a nasogastric tube. Other complications observed were: pleural effusion (3 patients), wound infection (2 patients), self-limited postoperative bleeding (2 patients), wound hematoma (1 patient) and diarrhea (1 patient). Two patients (5.7%) were readmitted due to intra-abdominal collections requiring radiological drainage and surgical reintervention respectively. Mean postoperative stay was 6.9 days (3-11 days). There was no mortality associated with the procedure.

DISCUSSION

The publication of the study by Kehlet in Lancet (33) has raised controversy about the classical attitude toward the postoperative management of surgically treated patients. The maxim of “wait and see”, with the surgeon being the subject who adapts to the events taking place in the postoperative period of the patient, has been transformed into a more active attitude (37-49).

Surgery for peritoneal carcinomatosis using peritonectomy procedures and the administration of intraoperative hyperthermic intraperitoneal chemotherapy is an aggressive type of surgery, performed on patients with advanced oncological disease occasionally underestimated by other groups and which has been subjected to multiple lines of chemotherapy prior to the surgical procedure. It is for this reason that the figures published for morbidity and mortality are high (morbidity around 30-50% and mortality related to the process of 1-5%) (28). However, not all the patients are subjected to cytoreduction procedures with the same intensity. Some patients only require pelvic surgery without the need to practice intestinal resections and anastomosis, although cytoreduction implies extensive peritoneal areas. In these patients, whose profile has been used in this program of fast track rehabilitation, it is possible to put accelerated recovery procedures into effect. Currently, there is no previous experience published in the literature about the peritoneal treatment of carcinomatosis using peritonectomies in a fast track

regime. In our series, 37 of the 46 patients included have fulfilled the protocol without any difficulty. The figures for morbidity and mortality were similar to those of other published series of patients with advanced ovarian carcinoma treated with maximum cytoreduction and HIPEC (Table 4).

Some authors opt for the non-use of abdominal drainage after surgery. We know that its use does not prevent anastomosis leaks and in addition it is generally removed before the days of greatest risk of producing them (52-54). In our series, pelvic drainage has only been used to prevent the formation of hematomas that could hinder the postoperative period. We have not carried out mechanical preparation of the colon in the preoperative period, basing our study on data published in colorectal surgery (55,56). Perioperative washing of the colon does not decrease the number of anastomotic leakages. In fact it is worsened in terms of greater morbidity and mortality due to the higher rates of hydroelectric alterations causing relative dehydration in our patients.

There is extensive experience in fast track programs in colorectal surgery. The basis of multimodal rehabilitation rests on two fundamental pillars in the postoperative period: early oral feeding and the early ambulation of the patient. There is no better stimulus for peristalsis than food (50, 51). Two meta-analysis studies confirmed that there is no role for their use in routine colon surgery (57, 58) nasogastric tubes delay discharge and increase pulmonary complications (59). The need for positioning the nasogastric tube due to vomiting when introducing orally administered food has been calculated to occur in at least 10% of cases (in our series 2 out of the 46 patients). The remaining 4 patients with paralytic ileus were treated without a nasogastric tube. Pharmacological help plays an important role, with the use of prokinetics such as metoclopramide and receptor inhibitors of serotonin which stop vomiting in the central area (ondansetron)

Premature ambulation is another fundamental point in fast track rehabilitation programs. It prevents the sensation of prolonged bed rest, a situation that occurs in most patients at least during the first 3 or 4 days in the immediate postoperative period, also having a beneficial effect on intestinal transit (60). This is one of the points the surgeon has to inform the patient about in the preoperative visit, given that otherwise the speed of events could be shocking. In our experience, there has been no problem with respect to

early mobilisation in the immediate postoperative period. The patient is lifted into the chair on the first postoperative day and even sometimes in the anesthetic resuscitation room.

Our preliminary data support the idea that in surgery for peritoneal carcinomatosis of ovarian origin with cytoreduction followed by HIPEC, the introduction of multimodal rehabilitation is reasonable in a group of selected patients with a low volume of carcinomatosis. However this is a small series requiring confirmation with prospective studies to establish the true role of this type of protocol.

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TABLES

Table 1. Patient characteristics

CHARACTERISTICS	Data
AGE	56.43 ± 10.56 years
PATIENT'S DISEASE STATUS (n° of patients and %)	
PRIMARY FIGO STAGE IIIC OVARIAN CANCER	35 (76%)
RECURRENT OVARIAN CANCER	11 (24%)
GOG PERFORMANCE STATUS	
0	19 (41%)
1	24 (53%)
2	3 (6%)
HISTOLOGIC TYPE	
SEROUS ADENOCARCINOMA	39 (85%)
ENDOMETRIOID ADENOCARCINOMA	3 (6.5%)
CLEAR CELL CARCINOMA	1 (2%)
OTHERS	3 (6.5%)
TUMOR DIFFERENTIATION	
WELL OR MODERATELY DIFFERENTIATED	21 (46%)
POORLY DIFFERENTIATED	25 (54%)

Table 2. PCI, surgical procedure, Completeness Cytoreductive Score (CCS), surgery time and hospital stay until discharge.

Peritoneal Cancer Index*	12.35 ± 3.96 (3-21)	
SURGICAL PROCEDURES	n	%
<i>LARGE OMENTUM</i>	39	84.8
<i>PELVIPERITONECTOMY (INCLUDING TH+BSO+DP)**</i>	37	80.4
<i>INTESTINAL RESECTION</i>	23	50
<i>RECTOSIGMOID</i>	14	30
<i>RIGHT COLECTOMY</i>	3	6.5
<i>SMALL BOWEL RESECTION</i>	6	13
<i>LYMPHADENECTOMY</i>	17	37
<i>PELVIC</i>	11	24
<i>PARAORTIC</i>	6	13
<i>RIGHT DIAPHRAGMATIC PERITONECTOMY</i>	8	17.4
<i>SPLEENECTOMY</i>	2	4.3
<i>LEFT DIAPHRAGMATIC PERITONECTOMY</i>	1	2.2
<i>URETER RESECTION</i>	1	2.2
COMPLETENESS CYTOREDUCTIVE SCORE	N	%
<i>CC-0</i>	38	82.6
<i>CC-1</i>	8	17.4
MEAN SURGICAL TIME (minutes) *	374.3 ± 83.2 (200-540)	
ADMISSION IN ICU (days)*	1.13 ± 0.49 (1-4)	
MEAN HOSPITAL STAY (days) *	6.94 ± 1.56 (3-11)	

* Expressed as mean ± standard deviation (range)

** TH+BSO+DP: Total Hysterectomy + Bilateral Salpingoophorectomy + Douglas Pouch resection

Table 3. Morbidity after surgical cytoreduction and HIPEC in advanced ovarian cancer.

MORBIDITY	GRADE			
	I-II	III	IV	TOTAL (n)
<i>Gastrointestinal tract</i>				
Diarrhea	1	-	-	7 (15.3)
Paralytic ileus	6*	-	-	
Anastomotic leak	-	-	-	
<i>Haemorrhage</i>				
Self-limited postoperative bleeding	2	-	-	3 (6.5)
Wound hematoma	1	-	-	
<i>Infections</i>				
Wound infection	-	2	-	4 (8.7)
Intraabdominal collections	-	1	1	
<i>Pulmonary complications</i>				
Pleural effusion	-	3	-	3 (6.5)
TOTAL (n)	10 (21.8)	6 (13.1)	1 (2.2)	17 (36.9)

* Only two patients needed a nasogastric tube

Table 4. PCI, Morbidity, mortality, type of drug used in HIPEC and hospital stay in some of the main studies published of patients with cytoreduction and HIPEC in advanced ovarian carcinoma and the present series.

AUTHOR	Year	n	PCI	DRUG-HIPEC	POSTOPERATIVE FAST-TRACK PROGRAM	MAJOR MORBIDITY (%)	MORTALITY (%)	MEDIAN LENGTH OF HOSPITAL STAY (DAYS)
ROVIELLO et al.	2010	53	<6	MITOMYCIN-C and CISPLATIN	NO	23	0	10
CEELEN et al.	2009	42	NA**	CISPLATIN or OXALIPLATIN	NO	21	0	16
PAVLOV et al.	2009	56	13.4	DOXORRUBICIN and CISPLATIN	NO	17.8*	2	14
DI GIORGIO et al.	2008	47	14.9	CISPLATIN	NO	21.3	4.2	22***
COTTE et al.	2007	81	11.5	CISPLATIN	NO	13.6	3	17***
RUFIAN et al.	2006	33	NA**	PACLITAXEL	NO	36*	0	11
PRESENT SERIES	2011	46	12.3**	PACLITAXEL	YES	15.3	0	6.9***

*TOTAL MORBIDITY RATES

**NOT AVAILABLE

*** RESULTS EXPRESSED AS MEAN