Neoadjuvant intraperitoneal chemotherapy with paclitaxel for the radical surgical treatment of peritoneal carcinomatosis in ovarian cancer: a prospective pilot study

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NEOADJUVANT INTRAPERITONEAL CHEMOTHERAPY WITH PACLITAXEL FOR THE RADICAL SURGICAL TREATMENT OF PERITONEAL CARCINOMATOSIS IN OVARIAN CANCER: A PROSPECTIVE PILOT STUDY

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ABSTRACT

PURPOSE: The admitted benefits of intraperitoneal chemotherapy during postoperative administration for the treatment of peritoneal carcinomatosis from ovarian origin are limited by their associated morbidity and restricted diffusion by the presence of multiple intraabdominal adherences. The purpose of the study was to evaluate the security, effectiveness and cytoreduction optimization of intraperitoneal paclitaxel administration previously to radical surgery/peritonectomy/HIPEC (Hyperthermic intraoperative intraperitoneal chemotherapy) either in monotherapy or combined with intravenous carboplatin. METHODS: Prospective pilot study of 10 patients with ovarian peritoneal carcinomatosis in stage IIIc-FIGO without previous treatment. After staging of the diseases by laparoscopy, five patients received paclitaxel by weekly intraperitoneal administration (60 mg/m^2, 10 cycles), and other five patients additionally received intravenous carboplatin every 21 days (AUC 6, 4 cycles). Subsequently radical surgery/peritonectomy with HIPEC was performed. RESULTS: The presence of moderate abdominal pain was the most common (70%) side effect associated to neoadjuvant paclitaxel intraperitoneal administration. The intravenous carboplatin administration was not associated with significant increase of adverse effects. It boosted intraperitoneal paclitaxel-associated antitumoral activity with a high average decrease of Index Cancer Peritoneal (21.2 vs 14.4, p=0.066) and CA 125(1053 vs 346, p=0.043). All the patients who received combined neoadjuvant chemotherapy obtained R0 cytoreduction. Five years overall survival was 62%. CONCLUSIONS: The intraperitoneal paclitaxel weekly administration combined with intravenous carboplatin administration prior to radical surgery/peritonectomy with HIPEC is a safe and effective option in the treatment of ovarian peritoneal carcinomatosis. This study shows the possibility to investigate other forms of intraperitoneal chemotherapy and their combinations thoroughly.

Word counts: 248

Key words: Intraperitoneal chemotherapy, neoadjuvant, paclitaxel, peritonectomy, ovarian cancer, morbidity.

INTRODUCTION

Ovarian carcinoma is the most frequent cause of death by gynecologic cancer in the developed world, and the fifth cause of death from cancer in women [1]. Approximately 70% of patients are diagnosed at advanced stages with peritoneal carcinomatosis. The development of surgical procedures by Sugarbaker which includes radical cytoreductive surgery with peritonectomy and the application of perioperative intraperitoneal chemotherapy has dramatically improved the prognosis of these patients [2,3]. The hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) administration with platin or taxanes derivatives after optimal cytoreduction is the most frequent modality of intraperitoneal chemotherapy used by oncological surgeons [4].

In order to improve the benefits of the intraperitoneal chemotherapy administration during surgical intervention, Sugarbaker has proposed the association with early postoperative intraperitoneal chemotherapy (EPIC) [3]. However, the associated morbidity of EPIC in colorectal carcinomatosis observed by Elias et al. [5] has limited its use. The intraperitoneal chemotherapy administration in advanced ovarian cancer has also been administered during the late postoperative phase. In this sense, there are randomized studies which show that intraperitoneal chemotherapy and intravenous combined administration improved the outcome when compared with intravenous isolated administration [6-8]. The administration of neoadjuvant intraperitoneal chemotherapy before radical surgery could achieve a better abdominal diffusion and treat non-visualized macroscopically areas or non-extirpated areas during surgery, with an increase of optimal cytoreduction.

The residual disease is the cause of frequent relapses and lethality in the patients. On the basis of this hypothesis, the present study analysed the security, effectiveness and cytoreduction optimization of the administration of neoadjuvant intraperitoneal chemotherapy, isolated or combined with intravenous chemotherapy in patients with ovarian peritoneal carcinomatosis stage IIIc-FIGO.

PATIENTS AND METHODS

Patients Eligibility

Ten patients with ovarian peritoneal carcinomatosis, without previous treatment related to their disease were included in a clinical prospective observational study. The inclusion of patients lasted from April 2004 to December 2009, and the patients were follow-up until June 2010.

The inclusion criteria were: 1) Histo-pathologic confirmation of peritoneal carcinomatosis from epithelial ovarian cancer (stage IIIc-FIGO), 2) Age ranged between 18 and 70 years old, 3) Performance status ≤2, and 4) Informed consent form filled out correctly.

The exclusion criteria were: 1) Extra-abdominal metastasis or IV stage of the FIGO, 2) previous treatment for ovarian carcinoma, either surgical or chemotherapic, 3) co-existence of another malignant neoplasm 4) renal, hepatic or cardio-vascular dysfunction, 5) intolerance or toxicity during the treatment and 6) unfulfillment of inclusion criteria. The selected patients were assigned to two groups of treatment of 5 patients each (Figure 1).

Diagnostic Laparoscopic-Stage and Intraperitoneal Catheter

The patients with suspicions of primary ovarian peritoneal carcinomatosis at stage IIIc-FIGO after the realization of chest-abdomen-pelvis CT and tumor marker (CA 125) were programmed for laparoscopic staging, calculation of PCI (Peritoneal Cancer index) [9] and histo-pathological confirmation with multiple biopsies. During the laparoscopic procedure, and after evacuating the ascitic fluid completely, Paclitaxel (60 mg/m^2) diluted in 2000 ml of saline solution during 60 minutes was administered intraperitoneally (Figure 1). A Tenckhoff® catheter (Sherwood Medical Company. Quinton Inc, Seattle, WA) was placed in the peritoneal cavity with subcutaneous exit and connected to the reservoir BardPort® (Bard Access Systems, Utah) once the cytostatic was evacuated. The reservoir was fixed over the front surface of the right iliac crest, for the weekly administration of intraperitoneal chemotherapy.

Neoadjuvant Chemotherapy

All patients were treated with ten cycles of intraperitoneal paclitaxel weekly administration (60 mg/m^2 diluted in 2000 ml of saline solution), starting two weeks after laparoscopy. The patients underwent positional changes immediately after intraperitoneal chemotherapy to ensure a better abdominal distribution. Five patients (including last) received a cycle of intravenous carboplatin administration immediately after laparoscopy followed by others in combination with the 2º, 5º and 8º cycles of intraperitoneal chemotherapy (Figure 1).

Radical Surgery Procedure and Postoperative Chemotherapy

Radical surgery with peritonectomy procedures including HIPEC was carried out one week after the 10th intraperitoneal chemotherapy cycle. Cytoreductive surgery degree was based on the classification described by the Gynecologic Oncologic Group (GOG) [10].

HIPEC was performed during 60 minutes after completed surgical resections following the usual procedure in our Center [11], with Paclitaxel (60mg/m^2 body surface) for every 2 liters of 1.5 % dextrose peritoneal dialysis solution. It was heated at 41-43ºC and infused at 800-1000 ml/minute.

The systemic adjuvant chemotherapy was based on six cycles administered every twenty-one days of carboplatin (AUC 6) combined with paclitaxel (175 mg/m^2) after radical cytoreduction surgery.

Variables analyzed

For the monitoring of the neoadjuvant period we analized different variables (abdominal pain, abdominal distention, nauseas, vomits, constipation, diarrhea, anorexia, asthenia, mucositis, alopecia, artralgias/myalgias, rubor/rash, angioedema, dyspnea, paresthesias, motor neuropathy, convulsions, encephalopathy and myelosupression or hematologic toxicity) which were graded according to CTCAE classification (Common Terminology Criteria for Adverse Events) v3.0 [12].

Biochemical variables were also determined to evaluate potential hidroelectrolitic, metabolic, renal or liver dysfunction: Urea, creatinine, sodium, potassium, chlorine, glucose, proteins, aminotransferase, LDH, and prothombin time. The tumor marker CA 125 was measured during all cycles of neoadjuvant chemotherapy. Peritoneal cancer index (PCI) were measured during laparoscopic and during the radical cytoreduction surgery. Other variables related to radical surgery were the procedure of peritonectomy, cytoreduction grade, intestinal resection, lymph nodes affection, postoperative morbidity, postoperative mortality, lenght stay hospital, disease relapse and overall survival.

Statistical analysis

Descriptive analysis included the measurement of mean ± standard deviation for quantitative variables, and proportions (%) for qualitative variables. Data were analized by Shapiro-Wilk test, Student´s test and Wilcoxon test included in the SPSS® 15.0 for Windows (SPSS Inc. Chicago, Illinois 606606). Regional relapse-free survival and overall survival were estimated from the date of surgery and

chemotherapy, using Kaplan-Meier´s analysis method. It was considered for statistical significant differences a 95% confidence interval ($p<0.05$).

RESULTS

Descriptive results

The global average age of the patients included in the study was of 49.8 ± 13.6 years old. Only two patients (20%) did not complete the neoadjuvant treatment, both included in the group of only intraperitoneal administration. Patient number one showed enterocutaneous fistula which required surgical intervention after the fifth cycle of intraperitoneal paclitaxel. Patient number four showed induration in the left breast, also after the fifth cycle of neoadjuvant intraperitoneal chemotherapy, proving the presence of ovarian carcinoma breast metastasis. This patient was excluded from the study. All patients who completed the neoadjuvant treatment (80%) eradicated the ascitis (Table 1).

Morbidity related to the use of the intraperitoneal catheter during neoadjunvancy was mild, and it was related to the presence of seroma (30 %). Nor infections from the perfusion system were detected neither other complications which supposed the interruption of the scheduled treatment, except for the subcutaneous fistula by tumor infiltration in the abdominal wall of the mentioned patient (Table 1). As regards morbidity related to neoadjuntant administered chemotherapy, moderate abdominal pain treated with standard analgesics, followed by the initial abdominal distention and asthenia, were the most remarkable secondary effects (Table 2). None of the patients showed fever, vomits, diarrhea, micturition syndrome, alopecia, mucositis, myalgias, angioedema, motor neurophaty, convulsions, encephalopaty or hematologic toxicity. There were no relevant changes in biochemical parameters.

Among covariables analyzed and exposed in Table 1, it was highly remarkable the scarce response of patient number 5. This patient did not change PCI or CA 125 marker, with a suboptimal cytoreduction-R2, despite total peritonectomy procedures.

The decrease of CA 125 was evident before and after treatment in both groups. The reduction of values of CA 125 was significant in the neoadjuvant combined group (1053.2±803.1 vs 346.8±546.1; $p=0.043$). However, differences were not significant in the isolated intraperitoneal group (528.5±408.4 vs 327.7±436.4; $p=0.326$). The mean values of PCI was also decreased in the neoadjuvant combined group (21.2±6.4 vs 14.4±4.8, $p=0.066$) and in the isolated intraperitoneal group (18±3.4 vs 14±6.5, $p=0.098$), although differences were not statistically significant.

Survival analysis

The global 5 years survival rate in the series of 9 patients included in the study was 62% estimated by the Kaplan-Meier's curve. The 67% (6/9) of the patients were alive and 56% (5/9) free of illness at the time of finishing this study with a global average monitoring of 39.1 ± 27.8 months (Figure 2).

DISCUSSION

The most relevant positive prognosis factor in the treatment of peritoneal ovarian carcinomatosis is the maximal cytoreduction [13]. We assume that it is necessary to incorporate peritonectomy procedures during radical cytoreductive surgery in order to increase the percentage of patients with optimal cytoreduction-R0, without residual macroscopical disease. These procedures eradicate macroscopic disease which typically invades the peritoneum of the abdominal cavity. The presence of residual disease not visible to the surgeon is responsible for tumor recurrence. In this sense, intraperitoneal chemotherapy has become a useful therapeutic strategy to obtain a total or maximum cytoreduction by elimination of the residual microscopic disease. The application of HIPEC is the most common method used for this purpose by the different groups of oncologic surgeons. The obtained results from this multidisciplinary approach have improved five years survival rate (60-70%) compared to those obtained previously in patients with optimal cytoreduction without HIPEC [14,15]. However, there are other different methods of intraperitoneal chemotherapy administration to enhance its therapeutic performance such as intraperitoneal chemotherapy administered during the first postoperative days or EPIC described by Sugarbaker. Other modality developed by the GOG is the administration in the postoperative period after discharge of the patient. However, different problems are associated with both options. In the first situation, extending intraperitoneal chemotherapy treatment immediately after aggressive surgery, as with EPIC, is too risky for debilitated patients. In the second situation, the effect of intraperitoneal chemotherapy is limited to a poor capacity of intraabdominal dissemination. In our study, intraperitoneal administration of chemotherapy before surgery for ovarian peritoneal carcinomatosis is an innovative and attractive procedure. The therapeutic sequence allows extending the loco-regional time action without morbidity associated from the early postoperative period or the inconvenience from the latest adherent postoperative syndrome, as well as increasing the benefits offered by neoadjuvant chemotherapy to the optimization of surgery [16] . We selected Paclitaxel by its well known antineoplasic

activity opposed to ovarian carcinoma, excellent pharmacokinetics when administered intraperitoneally, and the potential weekly administration [17,18]. The initial laparoscopic approach allows a better knowledge regarding the extension of the peritoneal disease (PCI) than CT, diagnosing its ovarian origin and histophatology [19]. It also allows evacuating ascites, to initiate immediately the neoadjuvant treatment and to place the intraperitoneal catheter for the weekly administration of paclitaxel.

The administration of intraperitoneal paclitaxel in monotherapy in the first five patients, and its association with intravenous carboplatin in the next five patients involved different monitoring time period in both groups (53.5 ± 35.7 months and 27.6 ± 14.7, respectively). The combined intravenous and intraperitoneal chemotherapy treatment allowed us to assess possible impact of desired effects in terms of antitumor efficacy and reduced potential adverse effects. The selected intravenous chemotherapy has demonstrated a neoadjuvant efficacy in ovarian cancer. The use of intravenous carboplatin monotherapy was based in the studies from the International Collaborative Ovarian Neoplasm Group in which no significant differences were observed between its intravenous administration in monotherapy compared with its combined administration with paclitaxel which is the standard chemotherapy in ovarian cancer.

The excellent tolerance of intraperitoneal neoadjuvant paclitaxel was due to its low associated morbidity, with abdominal pain of low-moderated intensity as the most frequent secondary effect controlled with standard analgesia, also probably due to the same malignant disease. The application of catheter induced the presence of non complicated seroma in the 30% of the patients that was solved with subsidiary punction-aspirations.

The eradication of the ascites in both groups (80% in intraperitoneal monotherapy group vs 100% in combined chemotherapy group) confirmed the previously showed potent anti-ascitic properties of paclitaxel. The antitumoral effect of the neoadjuvant chemotherapy was reflected in the decrease of PCI in both groups (60-80% of patients) although in the group of combined chemotherapy was more remarkable. The same occurred with CA 125 marker whose levels were normalized in three patients of this group. The regression of the peritoneal disease during this period of neoadjuvancy was confirmed during surgery and after histopathological evaluation of the samples.

The 100 % and 60% of patients completed the treatment in groups both combined and isolated intraperitoneal chemotherapy, respectively. Two patients from the last group did not complete the treatment by the presence of an enterocutaneous fistula, and by the late diagnose of stage IV breast metastasis. This case with distant metastasis was due to an underestimated staging, but not as excessive

tumor progression, taking into account the short period of time from diagnosis. This fact, together with the tumor postoperative progression towards lymphagitis carcinomatose with malignant pleural effusion from another patient of the isolated intraperitoneal chemotherapy group, showed us that diagnose methods of image used (TC) do not reach a sensibility of 100 % [19]. Consequently, the differentiation of the stage IIIc-FIGO from the stage IV can be fictitious. On the other hand, stage IIIc-FIGO in the ovarian carcinoma does not allow any distinction between patients with high or low degree of PCI and lymphatic nodes that are affected or not. In these cases, the administration of intraperitoneal neoadjuvant chemotherapy alone could be clearly insufficient.

Neoadjuvant combined chemotherapy showed a rate of 100% R0 cytoreduction. In the isolated intraperitoneal chemotherapy group was 50%. The absence of complication by carboplatin intravenous administration suggests that neoadjuvant therapy with intraperitoneal and intravenous carboplatin may be a useful approach for the treatment of patients in stage IIIc. The patients in stages IIIa-IIIb, with lower tumoral disease and absence of lymphatic affection, as well as with less possibility to be assigned to non-diagnosed stage IV could benefit themselves from intraperitoneal chemotherapy in monotherapy.

We can conclude that the neoadjuvant intraperitoneal treatment with paclitaxel was possible and safe, showing evident antitumoral effect. The association with intravenous carboplatin did not increase its secondary effects, being very well tolerated and with less adverse effects for the patients than those in which both were administered through intravenous via, such as alopecia or myelosupression. Although the limited sample size limited statistical comparisons between groups, the study demonstrated an overall 5 years survival rate of 62% and longer disease-free period for patients with ovarian peritoneal carcinomatosis (above 68 to 38 months). We might consider this new treatment option previously developed by Yonemura in advanced gastric cancer [20]. Furthermore, it shows that the combination of radical surgery/peritonectomy with HIPEC in peritoneal carcinomatosis ovarian allows the association with other forms of intraperitoneal chemotherapy. In this sense, the possible research lines of intraperitoneal chemotherapy and its potential combinations are still unexplored. The identification of the ideal time for chemotherapy administration should be a priority to increase the benefits of this therapy. This pilot study invites us to bear in mind this possible modality in the administration of neoadjuvant intraperitoneal chemotherapy and the laparoscopic approach used. Prospective larger studies are necessary to clarify many aspects about the real potential benefits of the neoadjuvant administration in association to radical cytoreductive surgery with HIPEC from ovarian peritoneal carcinomatosis.

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FIGURE LEGENDS

FIGURE 1. Schematic representation of the different phases of the study.

FIGURE 2. Kaplan-Meier´s overall survival rates of 9 patients with peritoneal carcinomatosis from primary ovarian cancer after neoadjuvant intraperitoneal paclitaxel (alone and in combination with intravenous carboplatin) and radical-peritonectomy and hypertermic intraoperative intraperitoneal chemotherapy (HIPEC).

TABLE 1: Covariates analyzed results in the intraperitoneal paclitaxel group (patients 1 to 5) and in the group of intraperitoneal and intravenous combined chemotherapy (patients 6 to 10). Neoadjuvant chemotherapy morbidity and postoperative morbidity was analized according to CTCAE classification v 3.0 [12].

PATIENT nº	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age (years)	58	60	50	47	65	46	32	24	49	65
Complete Treatment (≥75%)	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
IP chemotherapy cycles (Weeks)	5	10	10	5 (excluded)	10	10/4	9/3	10/4	10/4	10/4
Ascites before/after chemotherapy	Yes/No	Yes/No	Yes/No	Yes	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
PCI before/after chemotherapy	17/14	19/17	14/3	22	22/20	23/13	14/7	20/20	31/16	18/16*
CA 125 before/after chemotherapy	99/83	677/86	270/162	1452	951/980	1656/33	2142/1288	577/365	264/20	627/28
Catheter Morbidity	No	seroma	No	No	No	No	seroma	Seroma	No	No
Neoadjuvant Chemo Morbidity (Grades)	Enterocuta. fistula (G3)	Abdominal pain (G2)	Abdominal pain (G1)	Excluded from study Initial progression for stage IV-FIGO: Breast metastases secondary to ovarian cancer (treatment: intravenous chemothera. No surgery)	Abdominal pain (G2)	Abdominal pain (G1)	Abdominal pain (G2)	Abdominal pain (G2)	Abdominal pain (G2)	Abdominal pain (G2)
Cytoreduction Grade	R1	R0	R0		R2	R0	R0	R0	R0	Thorax CT: Thrombo-embolism Pleural effusion Stage IV-FIGO *Treatment: Anticoagu-lation + prolongation Intravenous Chemotherapy and after: Radical surgery/ peritonecto-my-HIPEC (R0)
Peritonectomy Procedure	Extended	Extended	Infraabdom		Total	Total	Total	Total	Total	
Intestinal Resection	Yes	No	No		Yes	Yes	No	No	Yes	
Positive lymph Nodes	Yes	No	No		Yes	Yes	No	Yes	No	
Postoperative Morbidity (Grade 3-5)	No	Grade 3	No		Grade 5	No	No	No	No	
Disease Relapse (Months)	12	36	No		SDRA-Lymphan-gitis carcino-matosa 18 day postop. Stage IV-FIGO	9	No	No	No	
Re-intervention for Relapse	Yes	No	No			Yes	No	No	No	
Length Stay Hospital (Days)	13	12	8			10	8	10	10	
Overall Survival (Months)	74	72	68			40	38	33	23	
Actual Status	Live	Live	Live			Dead	Live	Live	Live	

TABLE 2: Morbidity detected in both groups (intraperitoneal paclitaxel group and intraperitoneal/intravenous combined group) during the period of neoadjuvant, graded according to CTCAE classification (Common Terminology Criteria for Adverse Events) v3.0 [12]. G1: Grade 1. G2: Grade 2. G3: Grade 3.

Neoadj. Chemotherapy % Complications	Group Paclitaxel IP			Group Paclitaxel IP+ Carboplatin IV		
	G1	G2	G3	G1	G2	G3
Abdominal distention	40%	20%		80%		
Abdominal pain	40%	60%		20%	80%	
Nauseas	20%					
Constipation	20%	20%	20%			
Anorexia		20%				
Asthenia	60%			60%		
Rash	20%					
Cellulitis				20%		
Seroma		20%		20%	40%	
Dyspnea		20%		20%		
Paresthesia	20%					