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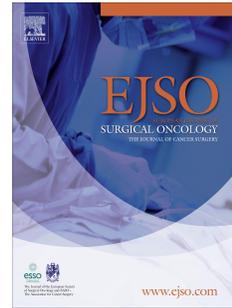
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Hyperthermic intra-peritoneal chemotherapy using Oxaliplatin as consolidation therapy for advanced epithelial ovarian carcinoma. Results of a phase II prospective multicentre trial. CHIPOVAC study.

Christophe Pomel 1, Gwenaël Ferron 2 , Gérard Lorimier 3, Annie Rey 4, Catherine Lhomme 4, Jean Marc Classe 5, JM Bereder 6, François Quenet 7, Pierre Meeus 8, Frederic Marshall 9, Philippe Morice 4, Dominique Elias 4.

1 *Centre Jean Perrin (Clermont-Ferrand)*

2 *Centre Claudius Regaud (Toulouse)*

3 *Centre Paul Papin (Angers)*

4 *Institut Gustave Roussy (Villejuif)*

5 *Centre René Gauducheau (Nantes)*

6 *Centre Antoine- Lacassagne et Centre Hospitalo-universitaire (Nice)*

7 *Centre Val d'Aurelle (Montpellier)*

8 *Centre Leon Berard (Lyon)*

9 *Centre Alexis Vautrin (Nancy)*

Email: christophe.pomel@cjp.fr

Corresponding adress:

Centre Jean Perrin

58 rue Montalembert

63000 Clermont-Ferrand

France

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ABSTRACT

Introduction

The aim of the present study was to prospectively evaluate morbidity of intra-peritoneal hyperthermic chemotherapy (HIPEC) using Oxaliplatin as consolidation therapy for advanced epithelial ovarian carcinoma and, secondly, to study peritoneal recurrence.

Methods

Between 2004 and 2007, 31 patients from 18 to 65 years with FIGO stage IIIC epithelial ovarian carcinoma were treated by surgery and a total of 6 cycles of platinum based chemotherapy. Those patients were eligible for consolidation therapy. We performed a second look laparotomy operation with intraperitoneal hyperthermic chemotherapy. We used Oxaliplatin 460 mg/m² with 2l/m² of saline solution in a open medial laparotomy for a total of 30 minutes at a temperature of 42-44 degrees celcius.

Results

The grade 3 morbidity rate was 29% (95 CI : 14%-45%). Nine patients experienced a total of 13 exploratory laparotomies for intra-abdominal bleeding after HIPEC. Two-year disease free and overall survival were 27% and 67% respectively. As a result of this high level of morbidity the trial was closed.

Conclusion

Using intraperitoneal Oxaliplatin associated with hyperthermia as consolidation therapy for advanced ovarian cancer results in a high risk of grade 3 morbidities with only a small benefit on survival.

Epithelial ovarian cancer (EOC) is usually discovered at an advanced stage resulting in an overall poor prognosis for this condition. Modern first line treatment with debulking surgery which is as complete as possible and an intravenous combination of Paclitaxel and Platinum chemotherapy can result in remission in a majority of cases. Unfortunately, 50% of optimally debulked patients will recur after a negative second look following 6 cycles of platinum based chemotherapy (1). Thus, overall survival will depend upon on 2 conditions: first, chemosensitivity and secondly, quality of cytoreductive surgery. Systemic treatment alone never results in cure, and so optimising surgery continues to be the best way to improve survival (2). Intra-peritoneal chemotherapy (IPC) after optimal debulking surgery has been demonstrated as being beneficial in terms of overall and disease free survival with acceptable quality of life (3, 4, 5). At this time a search for an effective consolidation treatment is required in order to control residual microscopic disease. So far none of the intra venous consolidation treatments have showed any survival benefits (6). The use of IPC as consolidation therapy is suggestive of a treatment benefit but does not support a change in clinical practice (7). On the other hand, IPC seems a very interesting and logical approach for a disease involving the peritoneal cavity. A consensus has emerged to support the potential benefit of hyperthermia associated with intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis from colorectal origin (8). Recent studies suggest some interest for the use of HIPEC in EOC patient (9). Standard HIPEC is used at the time of debulking surgery. We have designed a study aimed to evaluate the HIPEC related morbidity as consolidation therapy for EOC patients.

Between September 2004 and January 2007, we conducted a prospective non randomized multicentre phase 2 trial using hyperthermia and intra-peritoneal chemotherapy as consolidation therapy for advanced EOC. The trial was accepted by the local ethics committee. Informed consent was obtained from all patients. Oxaliplatin was used as a single agent. The main goal of the study was to examine the morbidity of this process, the secondary goal was to examine the overall survival and recurrence free survival. The design of the study was to enrol 67 patients for 2 years of inclusion and 5 years of follow-up. Statistical analysis was a Simon multistep "optimum design". The expected 20% grade 3 morbidity was considered to be acceptable. 40% was considered unacceptable. Morbidity was defined by Dindo classification (10). The study was planned in two steps with a minimum of 67 patients. Twenty eight at the first step and 39 at the second step. If the morbidity exceeded ten patients after inclusion and evaluation of the first 28 patients, then the study would be stopped. To be eligible for the study patients had Stage IIIC peritoneal carcinomatosis from ovarian, tubal or primary serous peritoneal adenocarcinoma including the following criteria:

- Patients aged from 18 to 65 years
- Patients that could not be optimally debulked at first look laparotomy and / or patients with positive second look after 6 cycles of platinum based chemotherapy.

Exclusion criteria was limited to patients of ASA 3.

All the patients presented normal preoperative coagulation state, normal preoperative platelets counts and no patients was taking antiaggregant therapy before the surgery. A laparotomy was performed after 6 cycles of platinum based chemotherapy. This procedure required a full abdominal adhesiolysis including small bowel, large bowel, posterior aspect of the liver and finally lesser sac to allow a complete immersion of the entire peritoneal cavity with HIPEC. The peritoneal extent was scored with the Peritoneal Cancer Index (PCI). At this stage a secondary cytoreductive surgery including peritonectomies according to Sugarbaker's techniques was accepted (11). If no disease remained or disease not exceeding one mm in the greatest diameter (volume) then an intraperitoneal hyperthermic chemotherapy was achieved. Four intraperitoneal temperature detectors were placed in the abdominal cavity, one in the right hypochondrium, one in the left hypochondrium, one in the pelvis and one in contact with the small bowel. We were

using Oxaliplatin 460 mg/m² with 2l/m² of saline solution in a open medial laparotomy for a total of 30 minutes with a 42-44° celcius degrees of temp erature. Anticoagulants such as fractionated heparin were used as thrombotic prophylaxis.

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Patients underwent surgery in eight different institutions. After 13 inclusions, 6 patients developed intra-abdominal bleeding. Therefore the dose of Oxaliplatin was reduced from 460mg/M² to 350mg/M². Analysis after 28 inclusions demonstrated that 13 emergency procedures were performed on 9 patients. The clinical trial was then closed. At the same time 3 more patients were registered before we closed the trial. Therefore our results involved 31 patients. Patient characteristics are summarised on table 1. Nine patients had optimal debulking at first look laparotomy. Twenty two patients had suboptimal debulking (more than 1cm residual tumour) at first look laparotomy. Thirty patients had 6 cycles of platinum and paclitaxel chemotherapy prior to the HIPEC and one patient had 8 cycles. PCI analysis observed at the beginning of the HIPEC laparotomy are reported on table 2. Twenty two patients had persistent disease at the time of the procedure. Nine patients had negative cytology with no residual disease. Limited cyto reduction without bowel resections performed at the time of the HIPEC could be completed for 16 patients. Six patients had less than 1mm residual tumour. Median operative time before the HIPEC started was 210 mn (70-700mn). Six patients received a blood transfusion at the time of the surgery.

Post operative course:

The grade 3 morbidity rate was 29% (95 CI : 14%-45%). Thirteen emergency laparotomies were performed on 9 patients for active intra-abdominal bleeding (IAB). Surgical characteristics of all patients with IAB are summarised on table 3. These surgeries were performed between post operative day 3 and day 12 (with a median of 8 day). Six patients had one exploratory laparotomy. Two patients had two exploratory laparotomies. One patient had three exploratory laparotomies. Among those 9 patients with IAB, median platelet levels were 88500 (54000 to 191000) This was not statistically different from the rest of the group study (42000-245000). No active bleeding was observed at the time of the exploratory laparotomies and one patient developed disseminated intravascular coagulopathy. One patient developed a coma with neurologic disorders and needed a tracheostomy. Five patients developed pulmonary infections. Median post op stay was 18 days range from 9 to 46 days. There was no difference of morbidity between 460 mg/M² (13 patients) and 350 mg/m² (18 patients) dose of Oxaliplatin. All

patients recovered completely. Overall and recurrence free survival are summarized on figure 1.

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To date 24 patients have developed a recurrence.

DISCUSSION

This trial assessing cytoreductive surgery plus HIPEC with oxaliplatin was prematurely closed as there had been an unacceptably high rate of re-surgery for peritoneal haemorrhage. To test this combined treatment for EOC was logical when considering that HIPEC using Oxaliplatin and surgical resection cured approximately 25% of patients with peritoneal carcinomatosis from colorectal origin. This strategy was mainly applicable to patients with limited intraperitoneal cancer volume and no extraperitoneal involvement (12). Platinum remains the most active drug class in ovarian cancer treatment. However, Oxaliplatin, a third-generation platinum derivative, has shown effective antitumor activity and a favorable toxicity profile in epithelial ovarian cancer (13). Consolidation/maintenance therapy in the standard management of EOC remains controversial, primarily due to the unknown impact of this strategy on overall survival. The use of HIPEC after 6 cycles of chemotherapy may represent an interesting approach as the peritoneal cavity has been previously treated both surgically and medically. Therefore this could minimize the amount of intra-peritoneal disease. This is extremely important as it has been demonstrated that the effect of HIPEC reaches the centre of tumour deposits less than 3mm (14). Extensive surgery associated with HIPEC usually impacts on morbidity. Therefore, our results reflect the side effects of HIPEC alone. 5 of the 8 centres involved in this study using HIPEC had more than 10 years of experience in this field. Unfortunately, in our series, surgical morbidity was a major issue. 9 patients developed post operative intra-abdominal bleeding (IAB) which was not incidentally associated with a less than 50000/ml platelets level. Other studies using Oxaliplatin for HIPEC in colon cancer patient regimen did not show such a dramatic risk of IAB. In the Gustave Roussy Institute, 90 patients were treated for peritoneal pseudomyxoma with

intraperitoneal oxaliplatin alone (460 mg/m² in 2 l/m² of iso-osmotic 5 per cent dextrose; 27 patients) or intraperitoneal oxaliplatin (360 mg/m²) plus intraperitoneal irinotecan (360 mg/m²) (63 patients), at a homogeneous intraperitoneal temperature of 43°C for 30 min. These 90 patients received an intravenous perfusion of 5-fluorouracil (5-FU) (400 mg/m²) with leucovorin (20 mg/m²) before starting HIPEC. Less than 5% of the patients developed post operative bleeding (15). Nevertheless, in a recent publication, Marcotte et al. observed an 18% risk of haemorrhage in a consecutive series of 38 patients treated by HIPEC with oxaliplatin at the same dose (16). Furthermore, Ceelin et al observed the case of one patient who developed unexplained repeated episodes of hemoperitoneum (17). This phenomenon occurred in three patients in our current series. Recently, Fagotto et al used the same dose of Oxaliplatin. After complete CRS they were submitted to intraperitoneal perfusion of oxaplatinum (460 mg/m²) heated to 41.5 °C for 30 min. The population of recurrent ovarian cancer patients with a platinum-free interval of at least 6 months were prospectively enrolled. Interestingly they observed 7 postoperative hemorrhage (18). Should we consider that 6 cycles of paclitaxel-platinum based chemotherapy prior to HIPEC may affect platelets toxicity? Does ovarian peritoneal carcinomatosis alter the coagulation system? We were unable to clearly answer to these questions. Unfortunately, the choice of Oxaliplatin with HIPEC does not appear to be a good option for EOC patients. Gori et al. investigated the effect of intraperitoneal hyperthermic perfusion chemotherapy as consolidation therapy in stage IIIB-IIIC epithelial ovarian cancer, following cytoreductive surgery and systemic chemotherapy (cisplatin-cyclophosphamide--six cycles). In a multicenter prospective trial, 29 patients with complete or optimal cytoreductive surgery and systemic treatment were included in the consolidation group and received HIPEC using cisplatin 100 mg/m², for 60 min. The consolidation therapy group showed a better 5-year survival rate and lower recurrent disease rate, but differences were not statistically significant (19). Furthermore, Kim JH et al. reported the study of 19 patients with stage Ic-IIIc EOC who

received consolidation intra-operative HIPEC using 6 L of lactated Ringer's solution containing paclitaxel 175 mg/m², for 90 min in hyperthermic phase. The survival rates were compared with 24 patients treated with conventional therapy. The 8-year overall survival rates were 84.21% in the HIPEC-paclitaxel group and 25.00% in the control group with a significant P value (20).

Our inclusion criteria included patients with poor prognostic factors: suboptimal (incomplete) debulking at first time laparotomy or positive second look. This could explain that overall and disease free survival rates are disappointing in this trial. Unfortunately HIPEC did not decrease the risk of peritoneal recurrence as 80% of our patients developed intra abdominal recurrence. As claimed in the recent paper of Helm et al, we still believe that HIPEC may be a future option in the management of advanced epithelial ovarian cancer. The choice of appropriate drugs will be the key point.

In conclusion, this phase II trial showed a dramatic rate of morbidity that fortunately did not affect perioperative mortality. We were unable to demonstrate any survival benefit following this therapy. Physicians should be aware of the possibility of acute intra-abdominal hematological emergencies following intra-peritoneal Oxaliplatin administration associated with hyperthermia in epithelial ovarian cancer patients. Therefore we would not recommend the use of Oxaliplatin in this indication.

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TABLE 1

Patients characteristics

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Epithelial ovarian cancer	28
Primary peritoneal cancer	3
Median age	57 (36-64)
Median weight (kilos)	60 (49-95)
ASA Score	0: 7 1: 5 2: 14

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Peritoneal Cancer Index analysis observed at the beginning of the laparotomy

Index	Nb pts
0	9
1-5	10
6-10	7
11-20	4
>20	1

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TABLE 3

Characteristics of all 9 patients with intraabdominal bleeding

Patients	Bigest deposit (cm)	PCI	Surgical procedure	Residual deposit	Experience of the Center in HIPEC (years)
1	5	30	Peritonectomies, Diaphragmatic stripping, cholecystectomy, appendicectomy, infragastric omentectomy, pelvic and PA lymphadenectomy	0	10
2	1	2	Infragastric omentectomy	0	4
3	0	0	Adhesiolysis	0	15
4	0	0	Adhesiolysis	0	15
5	0	0	Adhesiolysis	0	15
6	0	0	Adhesiolysis	0	10
7	2	19	Peritonectomies, diaphragmatic stripping, appendicectomy, completion of omentectomy, pelvic lymphadenectomy	0	4
8	0	0	Adhesiolysis	0	4
9	1	4	Infragastric omentectomy	0	8

FIGURE 1

Overall and Recurrence free survival

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