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Research Article

Feasibility and Outcomes of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Advanced Ovarian Cancer Stages: A French Pilot Study

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Abstract

Introduction: A recent trial has demonstrated that hyperthermic intraperitoneal chemotherapy (HIPEC) can improve survival of patients with advanced stages of epithelial ovarian cancer (EOC). However, its use remains a matter of debate due to the risk of complications. The aims of the present pilot study involving three French cancer expert centers were to evaluate the feasibility, intra- and postoperative complications, and survival after HIPEC.

Material and methods: We included 17 women with stage III-IV EOC treated by 3-4 cycles of neoadjuvant chemotherapy (NACT) in three French expert centers between January 2019 and July 2020 who underwent interval debulking surgery (IDS) with HIPEC: intra-abdominal temperature of 40°C, and infusion with cisplatin at a dose of 100 mg/m2 and flow rate of 1 L/min for 120 min.

Results: All the patients had a complete cytoreduction with no residual tumor. Lymphadenectomy was performed in seven (41.2%) patients. The Hudson procedure was performed in 13 (76.4%) patients. Rectosigmoidectomy, left, right and transverse colectomy, and small bowel resection were performed in three (17.6%), three (17.6%), two (11.8%), one (5.9%), and two (11.8%) patients, respectively. Among the 17 patients, five (29.4%) experienced a grade I-II complication according to Clavien-Dindo classification including urinary infection, pleural effusion, symptomatic hyponatremia, pulmonary infection and a clostridium colitis; and seven (41.2%) had a grade IIIA-B complication including acute kidney failure, hypovolemia caused by liver failure, sepsis inflammatory response syndrome after an acute pancreatitis infection, recurrent ascites, pneumothorax, and occlusion of the small bowel. No patient died postoperatively. During a median follow-up of 8 months (2-14.8), seven patients had a recurrence and two patients died.

Conclusion: Our data suggest that HIPEC after NACT and IDS is feasible and safe in patients with advanced EOC. Morbidity and mortality appear to be acceptable. These results could contribute to designing clinical trials to improve HIPEC administration in women with advanced stage EOC.

Keywords: Ovarian cancer; HIPEC; Chemotherapy

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Introduction

Epithelial ovarian cancer (EOC) is the second gynecological cancer in terms of mortality (207,252 deaths in 2020) after cervical cancer representing the eighth most common cancer worldwide (341,831 new cases in 2020) [1]. In France in 2018, 5193 women were diagnosed with EOC and 3479 died from the disease [2]. Most EOC (75%) are diagnosed at advanced stages (International Federation of Obstetrics & Gynecology (FIGO) stages III-IV) explaining the high associated surgical morbidity and mortality rates [1]. Although the 5-year survival rate for EOC has increased significantly during the last decades, thanks to new therapies such as poly(ADP-ribose) polymerase (PARP) inhibitors, the prognosis for all EOC stages remains poor with a 48.6% 5-year relative survival rate [3]. The standard of care of advanced EOC is based on surgery with the

aim of achieving complete cytoreduction, and chemotherapy with a platinum and taxane regimen [4,5]. The most powerful prognostic factor is complete surgery with no residual tumor [6]. For patients with residual tumor, bevacizumab, a recombinant humanized monoclonal IgG1 antibody targeting vascular endothelial growth factor-A, possibly combined with a PARP inhibitor, has been recommended due to high response rates and acceptable side effects [7]. Recently, the use of hyperthermic Intraperitoneal Chemotherapy (HIPEC), a selective drug delivery approach at the final step of cytoreduction surgery, has been advocated. The rationale is based on the hypothesis that HIPEC could be more effective than intravenous chemotherapy by eliminating residual microscopic peritoneal disease, and that hyperthermia increases the penetration of chemotherapy through the peritoneal surfaces. However, previous studies evaluating HIPEC after Primary Debulking Surgery (PDS) found no advantage on survival [8,9]. In 2018, a randomized trial, involving patients with stage III EOC after neoadjuvant platinum-based chemotherapy (3 cycles), compared Progression-Free Survival (PFS) and Overall Survival (OS) in a group of women who underwent HIPEC during Interval Debulking Surgery (IDS) with those who did not. Both PFS and OS were longer in the HIPEC group with no difference in side effects [10]. Subsequently to the publication of this trial, the French EOC guidelines recommend HIPEC after IDS but with strict compliance with van Driel's trial criteria [11]. Therefore, the aims of the present study were to evaluate (a) the feasibility, and (b) intra- and postoperative complications of HIPEC in women with advanced stage EOC in three French oncology centers.

Materials and Methods

Study population

From January 2019 to July 2020, the data of women with stage III-IV EOC receiving HIPEC after 3-4 cycles of Neoadjuvant Platinum-Based Chemotherapy (NACT) were retrospectively abstracted from prospectively maintained databases of three French university hospital oncology centers (Tenon Hospital, Poitiers Hospital, Rennes Hospital). All the women gave written consent to participate in the study. Eligibility criteria fulfilled those of the van Driel trial, i.e., women under 70 years old referred for neoadjuvant chemotherapy with a World Health Organization performance-status score of 0 to 2, normal renal function, and no toxicity related to taxane chemotherapy. The research protocol was approved by the Institutional Review Board of the French College of Obstetrics and Gynecology (CEROG 2020-GYN-0501).

Protocol

Patients were hospitalized 48h before surgery for hydration with 1L of physiologic serum IV. All the patients underwent a complete IDS with no macroscopic residual tumor followed by HIPEC delivered by the "open" (coliseum) or "closed" technique after satisfactory diuresis. The coliseum technique used in Tenon and Rennes Hospital consists of installing a Gray liver and upper organ retractor (Gray Surgical®, Bentley, Western Australia) for wide exposure, and stretching the skin to a ring support with 2-0 Vicryl sutures. A plastic iodophor drape (Ioban 2®, I3M Deutschland GmbH, Allemagne.) is attached to the frame to waterproof the system (Figure 1). For the closed technique used in Poitiers Hospital, at the end of the surgery, the 5 inflow and outflow silicone drains of the closed technique kit provided by Gamida® were disposed in the abdomen with one median inflow in the upper and lower part of the abdomen and 3 outflow (one under each side of the diaphragm and one in the middle of the abdomen, along the mesentery). For both techniques, the SUN CHIP II (Gamida®, Eaubonne, France) device is used. A saline solution is continuously circulating into the abdomen to maintain an intrabdominal temperature of 40°C (104°F). Simultaneously a perfusion of cisplatin (dose of 100 mg/m^2, flow rate of 1L/min) with 50% of the dose at first, then 25% after 30 minutes and 25% after 1 hour and a solution of sodium thiosulphate is administered with IV bolus (9 mg/m^2 in 200mL) to prevent nephrotoxicity. The HIPEC procedure takes 120 minutes in total, including 90minutes of the perfusion period. At the end of the perfusion, the abdomen is drained to empty the cavity. During all the procedure, the diuresis is maintained at a minimum of 1ml per kilogram per hour up to 3 hours after surgery. After the procedure, all the patients were admitted in the Intensive Care Unit for the first 48 postoperative hours.

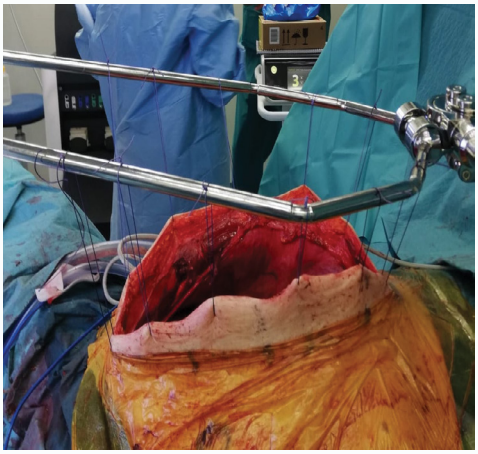

Figure 1: Hyperthermic intraperitoneal chemotherapy (HIPEC) "coliseum" installation. A Gray liver and upper organs retractor (GRAY SURGICAL®) and coliseum wires with Vicryl 2 is used to stretch the skin to the frame.

Data collection

The following preoperative patient characteristics were recorded: age, Body Mass Index (BMI), parity, previous surgery, familial and personal history of cancer, details of surgical procedures performed, size of retrieved specimens, and preoperative symptoms. Both intra- and postoperative complications were recorded and classified according to the Clavien-Dindo classification system as minor (grade I-II) or major (grade IIIA and IIIB-IV).

Results

Population characteristics

During the period study, 17 women with stage III-IV EOC were treated with HIPEC after 3-4 cycles of NACT (carboplatin and taxane): 4/17 (23.5%) were from Tenon University Hospital; 7/17 (41.1%) from Poitiers University Hospital; and 6/17 (35.3%) from Rennes University Hospital. The median age was 57 years (40-65) and the median BMI was 22.7 kg/m2 (17-27.9). BRCA-2 and BRAC-1 mutations were found in two (11.8%) and one (5.9%) patient, respectively. Histology confirmed high-grade serous adenocarcinoma in 16 (94.1%) patients and clear-cell carcinoma in one (5.9%). The median peritoneal cancer index (PCI) before NACT and at IDS were 13.5 (7-39) and nine (2-26), respectively. The clinical and histological characteristics of the population are reported in Table 1.

Cytoreductive surgery

The median time between the last chemotherapy cycle and the IDS with HIPEC was 27 days (21-84). Complete cytoreduction

Table 1: Clinical and histological characteristics of the population.

Characteristics (N= 17)	
Age (years) (median, range)	57 (40-65)
Body mass index (kg/m2) (median, range)	22.7 (17-27.9)
Menopause:	
Yes % (n)	88.2 (15)
No % (n)	5.9 (1)
NA % (n)	5.9 (1)
Family history of breast cancer % (n)	52.9 (9)
Family history of ovarian cancer % (n)	41.2 (7)
Genetic mutation:	
BRCA 1 % (n)	5.9 (1)
BRCA 2 % (n)	11.8 (2)
FIGO Stage:	
IIIA %(n)	11.8 (2)
IIIB %(n)	11.8 (2)
IIIC %(n)	41.2 (7)
IV %(n)	35.3 (6)
Histological type:	
Serous % (n)	94.1 (16)
Clear cells % (n)	5.9 (1)
CA 125 initial:	
<= 500 % (n)	41.2 (7)
> 500 % (n)	58.8 (10)
PCI initial (median, range):	13.5 (7-39)
PCI before IDS (median, range):	9 (2-26)
Number of cycles of neo adjuvant chemotherapy:	
3 cycles % (n):	41.2 (7)
4 cycles % (n):	58.8 (10)

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; PCI: Peritoneal Cancer Index

surgery with no residual tumor was achieved in all the patients. All the patients underwent hysterectomy and omentectomy. Additionally, appendicectomy, cholecystectomy and splenectomy were performed in 12 (70.6%), six (35.3%) and three (17.6%) patients, respectively. The Hudson procedure was performed in 13 (76.4%) patients. Lymphadenectomy was performed in seven (41.2%) patients. Perioperative outcomes are reported in Table 2. Rectosigmoidectomy, left, right and transverse colectomy and small bowel resection were performed in three (17.6%), three (17.6%), two (11.8%), one (5.9%), and two (11.8%) patients, respectively. Only two patients needed an ileostomy due to low anterior rectal resection. The median operating time was 450 minutes (330-600) including the 120 minutes required for HIPEC. The median blood loss was 1100 mL (300-3500). More than three-quarters of the patients (76.5%) received at least two units of red cell blood transfusion (0-5).

Characteristics of the HIPEC procedure

During HIPEC, all the patients had an intraabdominal temperature of 40°C (104°F) fully maintained with the complete protocol. No intraoperative complication linked to HIPEC was noted.

Surgical outcomes

The median stay in the ICU was 2.5 days (0-18), followed by 16 days (8-61) of hospitalization. During surgery, nine (52.9%) patients presented more than 1L of blood loss. No organ injury was reported during surgery. One patient presented a diaphragm breach which required pleural drainage in the ICU. Five (29.4%) patients did not have any complications. Five (29.4%) patients experienced a Clavien-Dindo grade I-II complication: urinary infection (1 case), pleural effusion (1 case), symptomatic hyponatremia (1 case), pulmonary infection (1 case), and a clostridium colitis treated by antibiotics (1

Table 2: Perioperative outcomes.

Surgical procedure:	
Hysterectomy % (n):	100 (17)
Omentectomy % (n):	100 (17)
Appendicectomy % (n):	70.6 (12)
Cholecystectomy % (n):	35.3 (6)
Diaphragm peritonectomy %(n):	47.1 (8)
Diaphragm resection % (n):	23.5 (4)
Splenectomy % (n):	17.6 (3)
Bowel resection:	
No % (n):	64.7 (11)
Bowel resection with ileostomy % (n):	11.8 (2)
Bowel resection without ileostomy % (n):	23.5 (4)
Median estimation of blood loss (ml):	1100 (300-3500)
Transfusion of blood %(n):	76.5 (13)
Median duration of surgery (min)	450 (330-600)
Median duration of hospitalization (days)	16 (8-61)
Median duration of ICU stays (days)	2.5 (0-18)
Early Complications:	
No % (n)	35.3 (6)
Yes % (n)	64.7 (11)
G1-G2 % (n)	23.5 (4)
G3 %(n)	35.3 (6)
G4 %(n)	0
Adjuvant chemotherapy % (n):	52.9% (9)
Bevacizumab % (n):	35.3 (6)
PARP inhibitor % (n):	17.6 (3)

Abbreviations: ICU: Intensive Care Unit; PARP: Poly ADP Ribose Polymerase

case). Seven (41.2%) patients experienced a grade IIIA-B complication: acute kidney failure due to drug toxicity with a favorable outcome without dialysis (grade IIIA, 1 case), hypovolemia caused by liver failure with also favorable outcome (grade IIIA, 2 cases), sepsis inflammatory response syndrome (SIRS) after an acute pancreatitis infection treated medically (grade IIIA, 1 case), recurrent ascites with no liver failure (grade IIIA, 1 case), pneumothorax after resection of a tumor infiltrating the diaphragm (grade IIIB, 1 case) requiring a pleural drainage in ICU, and occlusion of the small bowel by flange (grade IIIB, 1 case) treated by second surgery. No postoperative deaths were reported.

Short-term follow-up

The median time between surgery and adjuvant chemotherapy was 39.5 days (28-245 days). All the patients received adjuvant chemotherapy among whom seven (41.2%) received bevacizumab, and three (17.6%) a PARP inhibitor. The median follow-up was 8 months (2-14.8). During the study period, seven (41.2%) patients had a recurrence including two (11.8%) patients who died at 2 and 9 months after surgery. Recurrence disease modalities were liver metastasis (1 case), liver and paraortic lymph node metastasis (1 case), multiple metastases (2 cases), peritoneal carcinomatosis (2 cases), and a right diaphragmatic node (1 case).

Discussion

Our study demonstrates the feasibility and safety of HIPEC for patients with advanced stage EOC treated by 3-4 cycles of NACT followed by IDS in three experienced centers. Similarly to the OVHIPEC study, based on the National Comprehensive Cancer Network (NCCN) guidelines, we included newly diagnosed patients with advanced stage (III-IV) EOC pre-treated with NACT, which represents the population with the most promising results for HIPEC [12,13]. These patients have the most aggressive form of EOC and thus undergo comprehensive debulking surgery. In contrast, nearly a third of the patents in van Driel phase 3 multicentric randomized trial

comparing complete or optimal IDS with and without HIPEC had residual tumor or incomplete surgery [10]. Complete cytoreduction imposes multiple organ resection including bowel resection, extensive peritonectomy and splenectomy. In our study six (35.2%) of the patients underwent bowel resection which is similar to previous studies ranging from 18% to 58% in patients undergoing PDS or IDS without the use of HIPEC, but higher than that of van Driel trial (24%) [14,15]. Among the six patients requiring bowel resection, two (33%) underwent an ileostomy. This rate is also higher than that of van Driel trial (7%) and raises some specific concerns about performing an ileostomy in case of low rectal resection. Indeed, in agreement with previous studies, ileostomy carries with it specific morbidity reported in 30 to 60% of patients [16,17] and is associated with an altered quality of life and potentially delayed adjuvant therapies [18]. Another crucial issue of HIPEC is the rate of postoperative complications. In the present study, five (29.4%) patients experienced grade IIIA complications and (11.8%) grade IIIB. One patient underwent a second surgery for small bowel occlusion by flange without resection. No patients experienced a grade IV complication. These results are consistent with Chua systematic review of 19 studies of more than 10 patients reporting 0 to 40% of severe perioperative morbidity and 0 to 10% of mortality [19,20]. In our series, only one patient presented acute renal failure which resolved after administration of 1L of physiologic serum IV for hydration that inactivated circulating cisplatin without dialysis [21]. Overall, the complication rate after IDS associated with HIPEC in our study can be considered acceptable. As previously published, the time between cytoreductive surgery without HIPEC and adjuvant chemotherapy is a prognostic factor for PFS and OS [22]. The optimal interval is estimated between 6 and 8 weeks [22]. The median time to chemotherapy in our study was 39.5 days (28-245 days) which is similar to that reported by van Driel and Biacchi (33 days) [10,23]. Therefore, the use of HIPEC does not seem to delay adjuvant chemotherapy [24,25]. Adjuvant treatment for seven (41.2%) of our patients consisted of a combined platin-based chemotherapy (1 to 5 cycles) and bevacizumab with no reported side effects. This observation would seem to confirm the results of a phase II study showing the safety of bevacizumab therapy, approved by the Food and Drug Administration, after HIPEC in 40 patients with stage IIIB EOC [26]. However, we are waiting for the results from two ongoing prospective phase 3 trials –ICON7 and GOG-0218– to confirm whether bevacizumab is a suitable option after HIPEC for patients with advanced EOC [7,27]. In addition to chemotherapy, three (17.6%) of our patients received one of the PARP inhibitors olaparib or niraparib. All our patients with a BRCA mutation received maintenance treatment with olaparib following the protocol of the PAOLA-1 trial demonstrating a significant PFS benefit in this population [28]. Seven (41.2%) of our patients experienced recurrence during the study period which is a similar rate to previous studies (40.7% to 70%) [29-31]. Nevertheless, this result should be interpreted with caution as the median follow-up in our study was only 8 months which is too short to evaluate the recurrence rate. The strength of our study lies in its multicenter nature, homogeneous population and the involvement of experienced centers applying the latest recommendations. However, our study has two limitations. First, the small sample size. Originally, more patients were planned to undergo IDS and HIPEC during the study period but they had to be canceled due to the COVID-19 pandemic. The FRANCOGYN group of the National College of French Gynecologists and Obstetricians (CNGOF) convened to develop recommendations based on the consensus conference model for gynecological cancers [32-34]. Women with advanced EOC were considered to be at high risk of developing severe COVID-19 related morbidities especially linked to their stay in the ICU. Consequently, the recommendations were to delay cytoreductive surgery and, when surgery was planned, to avoid HIPEC [32-34]. Furthermore, HIPEC protocols are in competition with studies evaluating first-line treatments such as PARP inhibitors and bevacizumab. Nevertheless, our study clarifies ongoing concerns and confirms the safety and feasibility of HIPEC when performed in experienced centers. We therefore place HIPEC in a new perspective given the severe toxicity of new systemic therapies [35,36]. The second limitation is the short follow-up. However, our aim was to evaluate the feasibility of HIPEC, not the recurrence rate. Finally, our study could be the pioneer of clinicals trials evaluating the use of HIPEC as a first-line treatment for advanced EOC.

Conclusion

Our data suggest that HIPEC after NACT and IDS is feasible and safe in patients with advanced EOC. Morbidity and mortality due to hyperthermic perfusion and comprehensive surgery were limited and acceptable. HIPEC could follow the same trajectory as for colorectal cancer and mesothelioma and be administered as a complementary treatment in patients with advanced EOC after NACT.

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