Interval Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in First-Line Treatment for Advanced Ovarian Carcinoma

A Feasibility Study

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Objectives: We conducted a phase 2 trial to assess the feasibility of interval cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin in patients with stage III and IV pleural ovarian carcinoma in first-line treatment with no macroscopic residual disease after surgery.

Methods: Patients could be treated either with primary CS with HIPEC followed by 6 conventional cycles of chemotherapy or with 3 or 4 cycles of neoadjuvant chemotherapy before CS with HIPEC and 3 postoperative chemotherapy cycles. Hyperthermic intraperitoneal chemotherapy was performed with cisplatin (50 mg/m^2) for 60 minutes, only in case of complete cytoreduction.

Results: Nineteen patients were included in the study, and they all underwent neoadjuvant chemotherapy before CS. Sixteen patients underwent complete CS with HIPEC. There was no mortality, and morbidity of CS with HIPEC was acceptable. The HIPEC procedure did not prevent the administration of the standard first-line treatment. In the 16 patients who underwent CS with HIPEC, the outcomes were very good.

Conclusion: Our study shows an acceptable toxicity of adding HIPEC to the standard first-line treatment in patients with stage III ovarian carcinoma treated with interval CS. Further studies are needed to confirm the role of HIPEC in the treatment of ovarian carcinoma.

Key Words: Ovarian cancer, First-line treatment, Hyperthermic intraperitoneal chemotherapy (HIPEC)

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Ovarian carcinoma is the leading cause of death from gynecologic cancer in Western countries. Advanced disease is diagnosed in 75% of patients, with the disease mainly spread to the peritoneal cavity. Most of the patients achieve clinical remission after cytoreductive surgery (CS) combined with platinum- and paclitaxel-based chemotherapy

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but will relapse and die of the disease. The median progression-free survival (PFS) ranges from 17 to 30 months, and the median overall survival (OS) ranges from 36 to 65 months, depending on the volume of the residual disease after surgery.[1]

The way of administering chemotherapy was shown to be very important to improve survival. Indeed, the GOG 172 trial showed a dramatic improvement in OS (65.6 vs 49.7 months; hazard ratio [HR], 0.75; $P = 0.03$) in patients with stage III disease treated with intraperitoneal (IP) cisplatin and paclitaxel compared with those treated with intravenous administration.[2] According to the 3 available randomized trials, patients who benefit from an IP treatment are those with stage III ovarian cancer who have undergone optimal CS up to no or minimal residual disease.[2–4] The OS benefit (HR, 0.77) was sustained with a 10.7-year follow-up in a pooled analysis of two of those randomized trials.[5] Despite this improvement in OS, the IP chemotherapy is not widely accepted as standard therapy owing to a high rate of adverse effects and medical hesitations due to an increased complexity in providing IP chemotherapy.

Hyperthermic intraperitoneal chemotherapy (HIPEC) combines a high chemotherapeutic drug concentration in contact with the tumor cells, with the potential synergistic effect of hyperthermia (increased cellular metabolism and permeability).[6]

Several studies suggest that salvage therapy combining optimal CS and HIPEC may improve outcome in selected patients with recurrent ovarian carcinoma in whom optimal CS can be done,[7–16] with a mortality rate between 0% and 6% and grade 3/4 morbidity rates between 0% and 30% in technically experienced centers.

The first-line therapy is the only step of the disease when cure is the objective. In the GOG 172 trial, the survival benefit in the IP arm was obtained although half of the patients did not pursue the IP treatment over 3 courses owing to toxicity and changed to the standard intravenous arm. This highlighted the importance of administering IP chemotherapy early in the course of the disease.

Most data on HIPEC as first-line treatment are part of retrospective studies.[12,13,15,17–19] Six prospective feasibility trials have been published[20–25] in which patients were eligible for HIPEC after CS, even with a small volume of residual disease.

This pilot study was undertaken to assess the feasibility and toxicity of CS and HIPEC as part of the first-line treatment in patients with stage III and IV pleural ovarian carcinoma with no macroscopic residual disease after surgery.

PATIENTS AND METHODS

Study Design and Patients

Our prospective feasibility phase 2 study was conducted at the Institut Jules Bordet (Brussels) and at the Hôpital de la Citadelle (Liège) in Belgium from June 2010 to January 2015. Data were collected by the sponsor's team (Institut Jules Bordet, Brussels, Belgium) and analyzed by the Institut régional du Cancer de Montpellier (ICM) statistical team (Montpellier, France).

Eligible patients were 18 to 70 years old with laparoscopic initial staging, pathologically confirmed stage III or pleural stage IV ovarian carcinoma or primary peritoneal carcinoma or fallopian tube carcinoma. Patients had a performance status of 0 to 1 (World Health Organization [WHO]), adequate bone marrow, hepatic and renal functions, with no serious cardiac or respiratory illness, no major comorbidity such as uncontrolled diabetes. The protocol was approved by the institutional ethics committee of both centers and by the competent authority Eudract CT No. 2009-009467-59. All patients provided written informed consent before their participation in the study.

Study Treatment

Patients could be treated either with primary CS with HIPEC followed by 6 cycles of carboplatin-paclitaxel chemotherapy or, in case of initial advanced disease requiring more than 2 bowel resections or too extended to allow a complete CS, with preferably 3 cycles of neoadjuvant chemotherapy before CS with HIPEC, plus at least 3 postoperative chemotherapy cycles starting within 6 weeks after surgery.

Systemic chemotherapy consisted of carboplatin, area under the curve (AUC) 5 or 6, and paclitaxel, 175 mg/m^2 every 3 weeks.

Complete CS consisted of systematic hysterectomy, bilateral oophorectomy, complete omentectomy, pelvic and lomboaortic dissection, and removal of all macroscopically detectable lesions using surgical resection combined with electrofulguration after standard peritonectomy techniques (CC0: no macroscopic residual disease).[26]

Hyperthermic intraperitoneal chemotherapy was performed immediately after surgery using the open abdomen technique, with the skin in traction toward the top (Colyseum technique). When the target temperature (42°C) was reached with saline solution, cisplatin at the dose of 50 mg/m^2 was infused during 60 minutes, and intraperitoneal temperature at outflow was maintained between 42°C and 43°C.

Safety

Adverse events (AEs) during the treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0, including the AEs related to the surgical procedure.

In case of hematological and nonhematological AEs attributable to paclitaxel and carboplatin, a dose reduction was performed with a −20% (140 mg/m^2) or −40% (105 mg/m^2) recommended paclitaxel dose and an AUC 5 or AUC 4, respectively, for carboplatin dose.

End Points and Statistical Analysis

The primary end point was the evaluation of the rate of patients not dying of toxic death during the whole first-line treatment (success). Using an Optimum 2-stage Simon design with $\alpha = 0.10$ and $\beta = 0.20$, $P_0 = 0.80$, and $P_1 = 0.95$, 11 and 13 evaluable patients were required for the first stage and second stage, respectively. The treatment was to be considered sufficiently effective if at least 22 successes were reported among the 24 evaluable patients.

Secondary end points included treatment morbidity, PFS, and OS. The analysis was performed on an intent-to-treat

basis. All patients who started the treatment (neoadjuvant chemotherapy) were included in the safety analysis.

Concerning the descriptive analysis, quantitative variables were presented for each group and the overall population as medians and ranges. Qualitative variables were presented for each category of the variable with numbers and frequencies. Survival estimates were calculated using the Kaplan-Meier method. Disease progression was defined for each individual patient by the time from diagnosis to the date of investigator-assessed clinical or radiologic progression or death. Overall survival was defined by the time from diagnosis until death from any cause.

The analyses were made using the STATA v.13.0 software (StataCorp, College Station, TX).

RESULTS

Patients' Characteristics at Baseline

Nineteen patients were included in the study from June 2010 to January 2015 in 2 Belgian centers (Fig. 1). Owing to the recruitment being slower than expected, and after consultation with the principal investigator and the sponsor, the trial was stopped before the accrual of 24 patients. Safety data were therefore considered sufficient for the results analysis.

At baseline, 53% of the patients presented with comorbidities (cardiovascular, high blood pressure, and hypercholesterolemia). The median body mass index was 24.4 kg/m^2 (range, 19.9–33.3 kg/m^2); 5 patients were overweight and 2 had moderate obesity. Although patients could be treated with primary CS, all included patients were treated with 3 or 4 cycles of neoadjuvant chemotherapy because of too extended disease for primary CS without any macroscopic residue, which is required for HIPEC in this study. A too extended disease was defined as a disease requiring more than 2 bowel resections or too extended to allow a complete CS. All patients had stage III$_C$ (International Federation of Gynecology and Obstetrics [FIGO] 2009) disease. Patients' characteristics are detailed in Table 1.

TABLE 1. Patients' characteristics (n = 19)

Characteristics	
Median age at diagnosis (range), years	59 (31–67)
Performance status, n (%)	
0	10 (53)
1	9 (47)
Histologic type, n (%)	
Serous adenocarcinoma	18 (95)
Clear cell carcinoma	1 (5)
Histologic grade, n (%)	
3	19 (100)
Stage (FIGO 2009), n (%)	
IIIC	19 (100)
Therapeutic strategy, n (%)	
Neoadjuvant chemotherapy	19 (100)
No. neoadjuvant chemotherapy cycles, n (%)	
3	14 (74)
4	5 (26)

FIGO, International Federation of Gynecology and Obstetrics.

Cytoreductive Surgery and HIPEC

At the time of interval cytoreduction, median peritoneal carcinomatosis index was 12 (range, 3–34). Complete macroscopic tumor excision included complete or partial rectal or colic resection in 6 patients, partial small bowel resection in 3, splenectomy in 3, gall bladder resection in 8, and at least one peritonectomy in all patients.

Hyperthermic intraperitoneal chemotherapy was not performed in 3 patients; complete CS could not be achieved in one patient; for the 2 additional patients, CS was achieved but HIPEC could not be performed (anaphylactic shock for one and massive abdominal edema for the other).

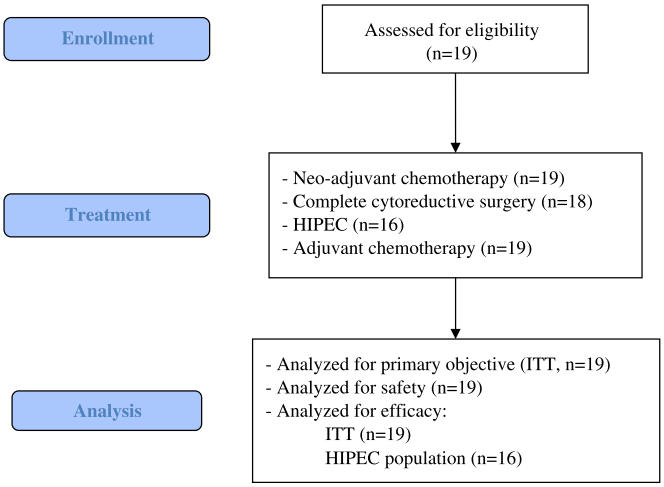

FIGURE 1. Study flow diagram. ITT, Intent-to-treat.

Sixteen patients had HIPEC with 50 mg/m^2 cisplatin infusion in the peritoneal cavity during 60 minutes at a 42°C inflow temperature.

Safety and Treatment Administration

The 19 patients were eligible for safety analysis. The median postoperative stay in the intensive care unit was 5 days (range, 1–10 days), and the median postoperative stay in the hospital was 15 days (range, 10–34 days). No patient died during the first-line treatment period. Grade 3 and 4 postoperative complications were encountered in 5 patients and resolved completely in 4 (Table 2). Among these, 2 patients needed secondary surgical revision, and one patient had a chronic renal insufficiency, which however, did not prevent the administration of postoperative chemotherapy.

The median delay between CS and the first postoperative chemotherapy cycle was 42 days (range, 14–89 days). Nine patients could not restart chemotherapy in the 6 required weeks. This delay was mostly due to postoperative complications of such a major surgery, which are also frequently reported in patients who do not undergo HIPEC. The longest delay, due to severe renal insufficiency reported in one patient, may be imputed more specifically to HIPEC itself.

All patients received a minimum of 6 cycles of chemotherapy. When 4 cycles were given preoperatively, 3 more cycles were given postoperatively. Four patients had a chemotherapy dose reduction during neoadjuvant chemotherapy, whereas no dose reduction was needed during the postoperative chemotherapeutic treatment.

Survival

At the moment of the trial analysis, 4 patients were dead and 10 disease progressions were recorded. After a median follow-up of 30.9 months, considering the whole population (n = 19), the median PFS was 33.2 months (95% confidence interval [CI], 12.9–36.4), with a 24-month PFS rate of 61.9% (95% CI, 33.9–80.8). The median OS was not reached, and the OS rate at 24 months was 85.2% (95% CI, 51.9–96.2; Fig. 2).

For the 16 patients who received HIPEC, the median follow-up was 25.5 months. In this population, the median PFS was 33.2 months (95% CI, 12.7–36.4), with a 24-month PFS rate of 69.2% (95% CI, 37.3–87.2). The median OS was not reached, and the OS rate at 24 months was 92.3% (95% CI, 56.6–98.9; Table 3).

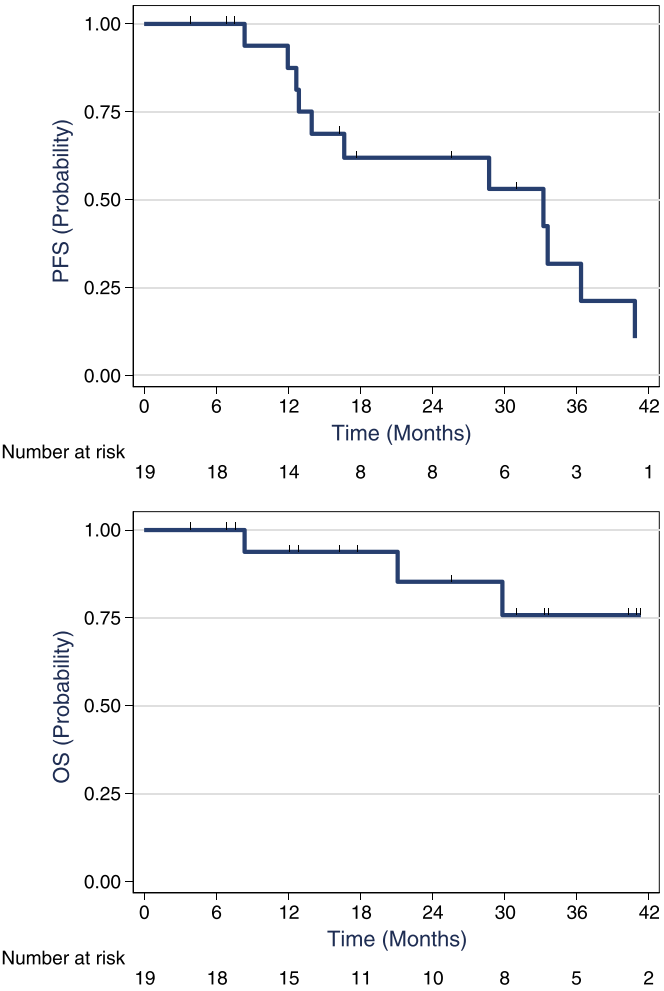

FIGURE 2. Progression-free survival and OS in the ITT population.

DISCUSSION

Our study shows an acceptable toxicity of adding HIPEC to the standard first-line treatment for patients with advanced stage III ovarian carcinoma treated with interval CS. To our knowledge, it is the first trial on HIPEC in first-line treatment requiring no macroscopic residue, that is, the most stringent definition of complete CS.

The small sample size due to insufficient patient enrollment (19 instead of the 24 expected) illustrates the difficulty of conducting HIPEC studies in ovarian carcinoma. Many centers have adopted the use of HIPEC in the treatment of ovarian carcinoma with peritoneal involvement despite the lack of significant data from well-conducted randomized trials either in first-line treatment or at the time of relapse.

TABLE 2. Grade 3 and grade 4 postoperative toxicities in the HIPEC population (n = 5/16)

Complication	Treatment	Evolution
Deep venous thrombosis	Anticoagulation	Complete resolution
Cardiac shock	Medical treatment	Complete resolution
Multifactorial acute renal failure	Temporary hemodialysis	Chronic renal insufficiency
Infectious peritonitis	Surgical drainage, antibiotics	Complete resolution
Bowel occlusion	Hematoma surgical drainage	Complete resolution

TABLE 3. Overall survival and PFS in the ITT and HIPEC populations

	No. Events	Median Months (95% CI)	Rate at 24 Months (95% CI)
ITT population (n = 19)			
OS	4	Not reached	85.2% (51.9–96.2)
PFS	11	33.2 (12.9–36.4)	61.9% (33.9–80.8)
HIPEC population (n = 16)			
OS	2	Not reached	92.3% (56.6–98.9)
PFS	9	33.2 (12.7–36.4)	69.2% (37.3–87.2)

ITT, Intent-to-treat; OS, overall survival; PFS, progression free survival.

Ongoing trials are therefore difficult to conduct. Moreover, in the first-line setting, trials assessing HIPEC are in competition with studies evaluating targeted therapies and systemic treatments. Thus, only half of the expected patients were really included.

The trial discontinuation did not permit to conclude on the primary objective; however, no toxic death was observed in the 19 included patients. The fact that the overall median survival was not reached indicates that events occurred slowly. Morbidity of CS with HIPEC was acceptable and did not seem superior to the morbidity of CS with the goal of no macroscopic residual disease. The perioperative management of these patients by very strict anesthetic, hemodynamic, and physiotherapy procedures seemed essential to control toxicities.

The HIPEC procedure did not prevent the administration of the standard first-line treatment, and the observed toxicities during postoperative intravenous chemotherapy were expected and usual for these patients. Only 16 patients were treated by HIPEC. Three were excluded owing to unfeasible complete CS (n = 1), anaphylactic shock (n = 1), or massive abdominal edema (n = 1). Among the 16 patients who underwent the whole procedure, the outcomes were very good, although the small study size does not allow any strong conclusion.

Our results are similar to those of other feasibility trials in first-line treatment, with regard to toxicity and tolerability.[20,21,23,24] These trials are too small, as ours, to validate the survival data of the patients. A recent meta-analysis of trials assessing HIPEC and CS in ovarian carcinoma has suggested an overall survival benefit for both primary and recurrent ovarian carcinoma.[27] However, those data still need to be clarified with the results of ongoing randomized clinical trials.

Unanswered questions remain regarding the procedure itself. Our study began with cisplatin 50 mg/m^2, and the dose was not changed during the study although higher doses of cisplatin are now used in advanced diseases. The drug of choice (cisplatin or carboplatin) and the optimal dose to be used have not been defined. Some other technical aspects still need to be addressed. For example, Liu et al[22] recently published their results in 20 patients testing aminolevulinic acid to help detect disseminated peritoneal disease, the goal being to allow a more complete tumor resection.

Moreover, the main question remaining is the optimal strategy for treating patients with advanced ovarian carcinoma in first-line, a crucial step of the therapeutic strategy, the only one when patient may be cured. Does HIPEC need to be added to a conventional standard treatment? Which of IP chemotherapy or HIPEC is preferable? Could they both be combined? What could be the strategy for patients for whom no optimal CS can be performed?

Meanwhile, many questions regarding quality of life (QoL) also need to be answered, although preliminary data suggest that the control of the disease is the main factor associated with a better QoL.[28] If validated, HIPEC will need to be more cautiously studied in the elderly populations, with adequate geriatric evaluation, since in this more fragile population, the procedure might be more toxic[29] and have a higher impact on the patients' QoL.

In conclusion, in accordance with previously published data, our results are encouraging and show a good appraisal of the HIPEC toxicity. This procedure thus should be tested as first-line treatment in larger clinical trials. Many questions remain, and further studies are needed to conclude on the possible integration of this procedure in ovarian cancer treatment. Reticence to participate in such trials seems unjustified. Efforts of the surgical and oncologic community are warranted to answer the crucial question of the role of HIPEC in the management of ovarian carcinoma in larger and randomized studies.

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