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Results of a multicenter phase I dose-finding trial of hyperthermic intraperitoneal cisplatin after neoadjuvant chemotherapy and complete cytoreductive surgery and followed by maintenance bevacizumab in initially unresectable ovarian cancer☆

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HIGHLIGHTS

- Phase 1 trial of HIPEC with dose escalation of cisplatin in ovarian cancer.
- Creatinine clearance decreased by 30 mL/mn or more in 15 of the 30 patients.
- We recommend a dose of 70 mg/m^2 of cisplatin for HIPEC.
- Diuresis should be maintained before HIPEC to reduce the risk of renal impairment.
- Bevacizumab appears to be feasible after cytoreductive surgery and HIPEC.

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ABSTRACT

Purpose. Hyperthermic intraperitoneal chemotherapy (HIPEC) may improve the outcome of patients with initially unresectable ovarian cancer who are eligible for complete cytoreductive surgery (CCRS) after neoadjuvant chemotherapy. The main objective of this multicenter phase-I study was to identify the recommended dose of cisplatin for HIPEC at CCRS after neoadjuvant carboplatin and paclitaxel (CP).

Methods. Patients were treated with 6 cycles of CP followed by CCRS and HIPEC using cisplatin heated for one hour at 42 °C +/− 1 °C. Four cisplatin dose-levels were evaluated: 50, 60, 70, 80 mg/m^2. Dose-limiting toxicities (DLTs) were defined as a grade ≥ IIIb adverse event (Dindo classification). The Continual Reassessment Method was used for this dose-finding study, with a target percentage of DLT set at 20%. Twenty-two cycles (15 mg/kg/cycle) of maintenance bevacizumab therapy were planned after surgery.

Results. Between June-2011 and September-2012, 30 patients were recruited. No DLT occurred at the first three dose-levels (4, 4 and 5 patients at 50, 60 and 70 mg/m^2 respectively). At dose-level 4 (80 mg/m^2, 17 patients), four DLTs occurred: renal failure ($n = 2$), peritonitis ($n = 1$) and hemorrhage ($n = 1$). Eight weeks after surgery, creatinine clearance was reduced to <30 mL/min in 3 patients, all treated at 80 mg/m^2, and between 30 and 60 mL/min in 6 patients (2, 1, 1 and 2 at the four dose-levels respectively). Twenty patients started maintenance bevacizumab, and 7 received the 22 courses initially planned.

Conclusions. Based on the observed DLTs and prolonged impairment of renal function, we recommend a dose of 70 mg/m^2 of cisplatin for HIPEC.

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1. Introduction

In most cases, ovarian cancer is discovered at an advanced and initially unresectable stage. The standard of care in advanced stage ovarian cancer (ASOC) combines complete cytoreductive surgery (CCRS) and systemic chemotherapy with a platinum agent. Unfortunately, progression-free survival is usually short, with an estimated median duration of 17 months in a French multicenter study [1]. To improve the prognosis of ASOC, three therapies were considered promising: intra-peritoneal chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) and bevacizumab. HIPEC is an attractive therapy against peritoneal carcinomatosis from ovarian cancer: after CCRS resecting the macroscopic peritoneal implants, HIPEC treats the remaining microscopic peritoneal implants. However, the exact place and modalities of HIPEC in ASOC remain to be defined. Intraperitoneal cisplatin chemotherapy has been shown significantly efficient as frontline treatment for ASOC in three large randomized studies [2–4]. Those three studies used intraperitoneal cisplatin capitalizing on its favorable peritoneal plasma gradient. Cisplatin is currently the reference agent for the treatment of ovarian cancer, as demonstrated in the meta-analysis reported by Aabo et al. [5] Adding hyperthermia to intraperitoneal cisplatin yielded direct cytotoxic and synergistic effects [6,7]. However, the cisplatin dose ranged from 25 mg/m2 to 150 mg/m2 in HIPEC used to treat ASOC. Moreover, these series were retrospective with heterogeneous patient cohorts [8]. Bevacizumab administered as maintenance adjuvant therapy significantly increased progression-free survival of patients with peritoneal carcinomatosis from ovarian cancer, as shown by two international randomized phase-III trials (GOG0218 and ICON 7) [9,10].

Considering the therapeutic impact of adding maintenance bevacizumab and the potential interest of HIPEC, the CHIPASTIN trial proposed a new therapeutic approach for ovarian cancer with initially unresectable peritoneal carcinomatosis. First, CCRS was performed after 6 cycles and not after 3 or 4 cycles of chemotherapy. Indeed CHIPASTIN proposed to include patients with important residual disease after 3 cycles. Second, bevacizumab maintenance therapy was performed after CCRS + HIPEC even if the surgery was macroscopically complete. Indeed, CHIPASTIN included only patients with high risk of recurrence due to the extension of disease after neoadjuvant chemotherapy. This new strategy combines CCRS with HIPEC, followed by a 15-month bevacizumab maintenance therapy. The CHIPASTIN trial included a dose-finding study for cisplatin administered in HIPEC, and the efficacy evaluation of the entire strategy.

2. Patients and methods

The study is an investigator-driven trial conducted in seven French comprehensive cancer centers, for initially unresectable ASOC.

The protocol was approved by the Ethics Committee and by the Competent Health Authority, and was registered in the ClinicalTrials.gov registry (NCT02217956). Written informed consent was obtained before surgery.

2.1. Patient eligibility

Patients aged between 18 and 65 with a confirmed histologic diagnosis of epithelial ovarian cancer were screened for the study if their disease was deemed unresectable at diagnosis (stage-IIIC according to the International Federation of Gynecology and Obstetrics) [11]. When the senior surgeon considered that a complete cytoreduction of the disease was impossible, patients received 6 cycles of neoadjuvant chemotherapy. They were included in the study if macroscopically CCRS was considered feasible (laparoscopy's and/or ct scan's results), providing all eligibility criteria were fulfilled. The main criteria were: 1) adequate renal function (creatinine <140 μmol/L, clearance >60 mL/min), bone marrow function (neutrophil count >1500/μL, platelets >150,000/μL), hepatic function (bilirubin ≤1.5×ULN, AST/ALT ≤1.5×ULN) and nutritional status (albumin >25 g/L); 2) No grade > 1 neuropathy (CTCAE-v4.0 classification); 3) No contraindication to bevacizumab administration.

2.2. Treatment plan

All patients were treated with 6 cycles of neoadjuvant chemotherapy combining carboplatin (area under curve, 5) and paclitaxel (175 mg/m2 every three weeks or 80 mg/m2 weekly). CCRS + HIPEC had to be performed within 10 weeks after the last injection of carboplatin. Cisplatin was administered intraperitoneally at a temperature of 42 °C +/− 1 °C throughout the abdominal cavity over 60 min. The cisplatin dose was defined according to the dose-escalation method. Four dose-levels were planned: 50, 60, 70, and 80 mg/m2. The study protocol recommended an hydratation to avoid a renal toxicity. Hydration began six hours before HIPEC to obtain a minimal diuresis (>0.5 mL/kg/h without diuretics) before, during and after HIPEC. Maintenance bevacizumab (15 mg/kg every 3 weeks × 22 cycles) was started 10 to 14 weeks after CCRS + HIPEC, for a total duration of maintenance therapy of 15 months.

2.3. Study endpoints

The primary endpoint of the trial was dose-limiting toxicity (DLT) within 30 days following CCRS + HIPEC. The following adverse events were classified as DLT: 1) Death; 2) Grade-IV toxicity according to the Dindo classification; [12] 3) Digestive, hepato-biliary or a pancreatic fistula requiring resurgery; 4) Severe bleeding (>30% blood mass) requiring resurgery; 5) an adverse event deemed life-threatening or resulting in a permanent disability.

The safety of CCRS + HIPEC was evaluated during hospitalization and at the visit planned at week-8 after CCRS + HIPEC, and included clinical assessment and biological tests on days 1, 3 and 5, then twice a week during hospitalization, then at week-8 (+/− 2 weeks). The safety of maintenance bevacizumab was evaluated before each new cycle and 4 weeks after the last administration. Creatinine clearance computed with the Cockcroft formula was monitored over the whole study duration according to the same schedule [13].

Toxicity occurring after CCRS + HIPEC and before week 8 was graded using the Dindo classification [12] and adverse events that occurred after week 8 were graded using the CTC-AE v4.0 classification [14]. The Data and Safety Monitoring Board (DSMB) of the study recommended a careful evaluation of renal impairment, in addition to the DLT monitoring.

To monitor the disease status, a clinical follow-up was performed at week-8, then every 3 weeks during maintenance therapy and every 4 months after the end of treatment until disease progression or death. CA125 and CA19.9 biomarkers were measured at week-8, at cycle-11, at the end of treatment, and every 4 months thereafter. A thoraco-abdominal CT scan was performed at the end of treatment and 12 months later, or when progression was suspected. Disease-free survival (DFS), defined as the time from CCRS + HIPEC to relapse or death from any cause, and overall survival (OS) defined as the time from CCRS + HIPEC to death from any cause were used as efficacy endpoints.

2.4. Statistical considerations

The dose-finding study was performed using the Continual Reassessment Method (CRM), with a one-parameter logistic model in a Bayesian framework [15]. After each new observation, the model was reassessed using all data previously collected. The dose-level recommended for the next patient was the one nearest to the 20% target percentile. Patients were included at the best ongoing estimate of the recommended dose (RD). Additional allocation rules were applied to ensure patient safety. Technical details are available in Appendix A.