Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(6): 143
https://doi.org/10.31083/j.ceog4906143

Review

HIPEC after Interval Debulking Surgery as Best Clinical Practice in Ovarian Cancer Patients: Case Series and Literature Review

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Academic Editor: Samir A. Farghaly
Submitted: 17 February 2022 Revised: 15 April 2022 Accepted: 26 April 2022 Published: 16 June 2022

Abstract

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) combined with interval debulking surgery (IDS) constitutes an adjunctive treatment strategy in advanced ovarian cancer (AOC). This approach is based on the concept of perfusing chemotherapy targeting directly the site of residual tumor after optimal surgical debulking. It improves patients' outcome in terms of overall survival (OS) and disease free survival (DFS). The correct selection of patients eligible for IDS + HIPEC is crucial: in particular, they must have shown a good response to neoadjuvant chemotherapy (NACT) and have a good performance status (PS). The application of HIPEC at the end of debulking does not seem to increase neither the rate of intra/postoperative complications nor the time of hospitalization. **Clinical Cases**: After approving an internal protocol for the application of HIPEC in our hospital, we have submitted four patients to IDS + HIPEC in the past 12 months. One of these patients underwent a minimally invasive procedure. No intra- or postoperative complications were observed. **Results**: All patients underwent IDS + HIPEC after being assessed as eligible and after showing a good response to NACT. In the course of IDS in all cases complete debulking was achieved. No patient developed intra- or postoperative complications. **Conclusions**: The addition of HIPEC to interval debulking surgery should be offered to all eligible patients, considering that the association of HIPEC to IDS seems to improve patients' outcomes in terms of OS and DFS, without increasing post-operative morbidity .

Keywords: advanced ovarian cancer; HIPEC; interval debulking surgery

1. Introduction

Ovarian cancer is the leading cause of death among gynecologic malignancies [1]. It is responsible for 5% of all cancer deaths in women worldwide [2] and it seems to be correlated with the human development index [3]. Due to the lack of a screening method for ovarian cancer and its frequent absence of symptoms, most patients come to medical attention in an advanced stage of illness (stage III/IV), commonly with peritoneal metastases and concurrent ascites [4]. The most common route of spread for ovarian cancer is within the abdominal cavity, often with diffuse metastatic disease involving the peritoneum at the time of diagnosis [5,6]. The gold standard of treatment remains primary debulking surgery (PDS) if feasible, although neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is a good option for patients considered to have unresectable disease at onset [7,8]. Therefore, at the time of diagnosis, it is useful to perform a diagnostic laparoscopy to define the possibilities of optimal debulking and carefully select patients for debulking surgery [9,10]. In case of diffuse disease (Fagotti's score >8) [11] or high risk of postoperative complications (Vizzielli's score >6) [12], it is not advisable to continue with the debulking attempt. It is recommended to perform one or more biopsies to define histology, molecular biology, and possible genetic mutations [13]. Interval debulking surgery would be preferable for patients with unresectable disease at onset [14]. According to the most recent literature, in this particular subset of patients, with a non-inferior oncological outcome, IDS would be burdened by a lower rate of post-operative complications than a PDS [15]. The application of HIPEC after debulking inevitably prolongs the median surgical time but

does not show an increase in intra- and post-operative complications [16]. No differences have been identified regarding the onset of postoperative chemotherapy and it does not compromise the fulfillment of chemotherapy cycles [16].

However, even after complete resection of the tumor, 60%–70% of patients present recurrence of the disease, mainly in the peritoneal site [14]. With the goal of prolonging both disease-free survival (DFS) and overall survival (OS), several new combinations/therapeutic approaches have been investigated, including antiangiogenic therapy, target therapy (PARP-I), immunotherapy, and HIPEC. The use of HIPEC as a strategy to address the spread of the peritoneal disease has been investigated in both primary and relapse treatment settings [17,18]. The surgical outcome and the overall survival are also correlated to several variables: (1) tumor-related variables, such as the localization and size of the disease as well as its biological features; (2) patients' related factors, in particular performance status and co-morbidities. The amount of residual tumor after surgery is a major predictor of survival, and it is probably the only modifiable factor [19]. A key element, that allows this procedure to become part of the clinical practice, is to create a multidisciplinary team with the aim of improving the treatment plan and care for all patients with ovarian cancer [20]. Different surgical and medical specialists should be engaged to get a stratification of patients in different prognostic groups, and consequently different treatment approaches. Taking into account the importance of proper preoperative patient selection, as reported in literature, in our hospital, we use both a preoperative and intraoperative evaluation: the first one during a multidisciplinary meeting, involving multiple specialists needed to assess the patient; the second using established algorithms that take into consideration the patient's characteristics and tumor dissemination during the surgical exploration using Fagotti's and Vizzielli's scores. These strategies allow getting the best selection of patients for surgery. Moreover, only patients for whom the clinical and radiological response is defined as at least good at the preliminary multidisciplinary meeting are proposed for IDS + HIPEC.

2. Clinical Cases

We present a case series of four patients treated in our hospital with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) after interval debulking surgery (IDS), supporting this combined treatment as best clinical practice in patients with advanced ovarian cancer (AOC) previously submitted to neoadjuvant chemotherapy (NACT). IDS refers precisely to the timing of the surgery between two chemotherapies, and according to ESGO guidelines we consider the term debulking as cytoreduction.

According to our internal protocol, four patients underwent IDS + HIPEC in the last year in our hospital. They were paucisymptomatic at the diagnosis, with abdominal swelling and increasing asthenia. The mean age of the patients was 56.25 years (range 49–63). Clinical characteristics of the patients are summarized in Table 1. The ECOG performance status was 1 for all patients. For three women, a diagnostic laparoscopy with biopsy was performed, applying Fagotti's and Vizzielli's scoring system to determine if debulking was feasible. In one case Fagotti's score was 12 and Vizzielli's score was 7, in the other case Fagotti's score was 12 and Vizzielli's score was 6. In the third case Fagotti's score was 8 and Vizzielli's score was 4, so a PDS surgery had been started and then suspended due to the onset of anesthesiologic problems, so it was then decided to start chemotherapy. In one patient, surgery was performed in another hospital and the scoring was not applied. The histological examination of biopsies performed during laparoscopy confirmed high-grade serous carcinoma of the ovary in all cases. According to the recent guidelines these patients underwent NACT. After three cycles of carbo platinum + paclitaxel infusion, the patients were reassessed. The mean value of CA 125 before start chemotherapy was 785.85 UI/mL (range 702.2–879.6), while after chemotherapy it was 41.65 UI/mL (range 11.4–92.6), with a median decrease of 95% (range 89.5% vs 98.4%) from the starting point. Also, imaging results confirmed a good response to NACT. After discussing each case at the multidisciplinary meeting, considering the biochemical and radiological results and the performance status of the patients, they were considered eligible for IDS + HIPEC. In all treated patients a complete debulking was obtained with residual tumor 0 (RT = 0). Two patients showed no macroscopic peritoneal involvement, so we did not excise the normal-looking peritoneum, whereas the other two patients had a peritoneal involvement on the right diaphragmatic side and in the Douglas pouch. Among the different peritonectomy techniques [21], we chose to remove the only affected areas using a transperitoneal approach achieving a selective peritonectomy: this approach permits treat this subset of patients without increasing perioperative morbidity resulting from a total peritonectomy of 'normal-looking' peritoneum [22,23]. For the two cases in which we perform a right diaphragmatic peritonectomy, we followed the standardized procedure stripping the peritoneum away from the posterior sheath using a ball-tipped electrosurgery after cutting the falciform ligament of the liver [24,25]. One of the patients underwent a minimally invasive debulking, without any complication. The surgical complexity score (SCS) was 2 for three patients and 1 for one patient. Regarding BRCA mutational status, only one patient showed both BRCA 1 and BRCA 2 mutations, two other patients had only BRCA 1 mutation. No intra- nor post-operative complications were observed. Moreover no 90-days post-operative complications, according to the ClavienDindo Classification, were reported. Currently, all the women are alive and have not developed any complication.

Table 1. Patient's characteristics.

Case num.	1	2	3	4
Age at diagnosis (y)	53	63	49	60
Age at the time of HIPEC	53	63	50	60
Date of diagnostic LPS	06/08/21	20/08/21	16/09/21	07/09/21
First CHT cycle	20/08/21	02/09/21	03/10/21	05/10/21
Fagotti's score	12	12	/	8
Vizzielli's score	6	7	/	4
Date of surgery	08/11/21	22/11/21	20/12/21	31/01/22
Type of surgery	LPT	LPT	LPS	LPT
Last CHT cycle	01/10/21	15/10/21	23/11/21	07/12/21
CA 125 (1)	879.6	835.8	702.2	725.8
CA 125 (2)	92.6	30.8	11.4	31.8
Histotype	serous	serous	serous	serous
Grade	high	high	high	high
FIGO stage	IIIC	IIIC	IIIC	IIIC
ECOG PS	1	1	1	1
Complete debulking	yes	yes	yes	yes
BRCA 1 mutation	yes	yes	no	yes
BRCA 2 mutation	no	no	no	yes
SCS	2	2	1	2
PCI score during LPS	/	/	/	/
PCI score during IDS	/	/	/	/
Duration of HIPEC (min)	90	90	90	90
Drug used for HIPEC	cisplatin 100 mg/m^2	cisplatin 100 mg/m^2	cisplatin 100 mg/m^2	cisplatin 100 mg/m^2
Temperature during HIPEC	40 °C (104 °F)	40 °C (104 °F)	40 °C (104 °F)	40 °C (104 °F)
Disease free survival (months)	4	4	3	1

LPS, laparoscopy; CHT, chemotherapy; CA 125 (T_0), CA 125 value before NACT; CA 125 (T_{IDS}), CA 125 value at IDS; ECOG PS, Eastern Cooperative Oncology Group Performance Status; SCS, Surgical Complexity Scale; PCI, Peritoneal Cancer Index.

3. Discussion

The role of HIPEC is supported by the principle that chemotherapy administered directly at the tumor site can increase the cytotoxic effect of the drug itself [26]. HIPEC has an advantage in terms of pharmacodynamics compared with intravenous administration of chemotherapy. Indeed, intraperitoneal diffusion combined with heat effect seems to improve the uptake of chemotherapy and the susceptibility of tumor cells, allows the permanence of chemotherapy in contact with the peritoneal surface, and increases the concentration of chemotherapy without increasing its toxic effects [27].

It is clear the relevance of performing a careful selection of patients eligible for HIPEC to achieve the maximum benefit of the procedure without exposing the patient to increased perioperative risk. According to our protocol, patients should be considered not eligible for HIPEC if: body mass index (BMI) >35 kg/m^2; age <18 or >70; insufficient clinical/radiological response to chemotherapy; recent or synchronous diagnosis of another tumor; active infection; poor clinical condition or ECOG performance status >1; intestinal occlusion; medical conditions that may interfere with treatment (in particular creatinine clearance <60 mL/min according to Cockroft-Gault, neutrophil count <1500/mL, platelet count $<150,000$/mL); anti-angiogenic drugs discontinued less than six weeks.

At the end of IDS, the patient is eligible for HIPEC only if optimal debulking has been performed with a residual tumor burden (RT) <1.0 mm (RT 0/1) [10]. If the patient meets the criteria, following our protocol, we started perfusion of Cisplatin 100 mg/m^2 with closed technique at an average temperature of 40 °C (104 °F) for an effective perfusion time of 90 minutes. To avoid nephrotoxicity of the chemotherapic drug it is recommended to infuse sodium thiosulfate 9 g/m^2 in 200 mL at the beginning of perfusion followed by a continuous infusion of 12 g/m^2 in 1000 mL for 6 hours. During the procedure and in the subsequent hours it is necessary to control diuresis by keeping it around 1/mL/kg/h ensuring adequate hydration of the patient. Other parameters to be checked intraoperatively and postoperatively are hematocrit and hemoglobin (Hct 27%, Hb 8.5 g/dL) body temperature and pH to avoid coagulation disorders.

The most informative study demonstrating significant survival benefit for AOC patients undergoing IDS and HIPEC was a Phase III trial by Van Driel *et al*. [28] published in the New England Journal of Medicine in 2018. The authors randomly assigned 245 newly diagnosed, stage

III epithelial ovarian cancer patients who had at least stable disease after three cycles of NACT with carboplatin and paclitaxel to undergo IDS either with or without HIPEC. The primary end point of the study was to compare the median progression free survival (PFS) in the two groups: PFS was 10.7 months for patients in the standard arm compared with 14.2 months for those in the HIPEC arm (HR, 0.66; 95% CI, 0.50–0.87; $p = 0.003$). No differences in postoperative complications were found in the two groups. Among the strengths of this study it is important to highlight that the median PFS and overall survival (OS) in the control arm were overlapping to those of previous randomized clinical trials that included similar patients. The study by Van Driel *et al*. [28] was the first randomized trial in which the only difference between the two groups was the use of 90-minute intraperitoneal cisplatin perfusion after surgery. However, the results of this trial have been questioned by several authors, listing among its limitations the improper sample size calculation before the beginning of the study, the long recruitment period of over 9 years, the potential randomization bias by pre-operatory randomization, and the toxicity rate in the HIPEC arm. Nevertheless, considering the good results of the OVHIPEC trial, the National Comprehensive Cancer Network in 2019 updated guidelines in which it proposes as the first-choice treatment for patients with stage III ovarian cancer undergoing IDS the use of HIPEC at the end of surgery [29].

Previously in 2017 Di Giorgio *et al*. [30] published a retrospective multicenter observational study that recruited a large number of patients (n = 511) diagnosed with primary or recurrent ovarian cancer, undergoing debulking surgery combined with HIPEC. Data included results from both PDS and IDS combined with HIPEC with a similar percentage of patients treated for primary or relapsed ovarian cancer (70.8% vs 74%). Analyzing data from the IDS group, the authors found that patients who had shown a good response to NACT, compared to those who had undergone IDS with no response to NACT, got a better overall survival rate (OS 47.6% vs 24.6%, median 58 vs 37, 4 months; $p <$ 0.007). In this study, HIPEC technique was applied to all patients undergoing IDS: they did not select patients on the base of the response to NACT, this constitutes a limit of the study, associated with the use of different HIPEC protocols applied in several centers involved. These results have allowed further investigations to get a correct selection of patients in which HIPEC application can improve outcomes.

A recent review and meta-analysis on the application of HIPEC in AOC by Wang *et al*. [31] analyzed 13 papers showed that the addition of HIPEC to debulking surgery both for primary and recurrent ovarian cancer patients could significantly improve OS and DFS with tolerable toxicity, morbidity, mortality, and quality of life outcomes. However, the subgroup of recurrent ovarian cancer exhibited no statistical significance in DFS. In addition, the study also demonstrated that 90min HIPEC significantly improved both OS and disease-free survival (DFS) for ovarian cancer patients [31].

Regarding the incorporation of paclitaxel-based HIPEC, 40 patients were recruited in a trial proposed by Lee YJ *et al*. [32] with the primary endpoint of assessing PFS in patients with AOC (FIGO stage III–IV) who underwent IDS + paclitaxel-based HIPEC. Median PFS in the group of patients who received HIPEC was reported to be similar to that of patients receiving NACT (19.7 vs 21.3 months). This study, despite the limited sample size and the short follow up period, provided the feasibility of the paclitaxel based HIPEC technique with acceptable toxicity, underling the importance of a correct selection of patients eligible for HIPEC, in particular, the better results are seen in women who had had a good response to chemotherapy [32].

In conclusion, the standard treatment for AOC remains the PDS with RT = 0, if it is impossible to obtain complete cytoreduction in first instance, the best practice is to start NACT and re-evaluate the clinical response. It is important to select patients with good response to NACT and give an indication to IDS + HIPEC if the patient is eligible. According to the literature, in our center we applied HIPEC after complete debulking surgery in patients previously treated with NACT: our case series represent an example of feasibility of the technique and best clinical practice in this specific topic. Interestingly, this seems to improve DFS without increasing perioperative complications, as confirmed by Ghirardi *et al*. [16]. This paper is the first real-life experience after the publication of the OVHIPEC trial and it gives further support to the application of HIPEC in the setting of IDS, confirming that it does not increase the complication rate nor the hospitalization period, emphasizing the importance of correct and careful patients' selection [16].

It is well known that the rationale for the use of intraperitoneal therapy is the direct contact of the drug with the peritoneal surface, increasing its concentration in the tissues [27]. Based on this issue, the rate of abdominal and extra-abdominal recurrences in patients treated with HIPEC was investigated. In 2021 Chambers *et al*. [33] published a single-institution cohort study on women with AOC who underwent HIPEC during surgery. A total of 92 women were recruited, of whom 52 underwent IDS + HIPEC and 40 underwent recurrent debulking surgery + HIPEC. Their findings suggest that HIPEC may improve disease control within the abdomen due to the treatment of the peritoneal surfaces [34].

Concerning the surgical technique, HIPEC can be used both during classic open and minimally invasive surgery (MIS). Therefore, in instances where the gynecologic oncologist believes it is possible to achieve optimal debulking by MIS, the use of HIPEC should not be a limitation as claimed in a retrospective cohort study on fifty women with high-grade FIGO stage III–IV epithelial

ovarian, fallopian tube, and primary peritoneal carcinomas by Morton *et al*. [34]. In their study, 10 patients underwent MIS and 40 had classical laparotomy, both combined with HIPEC. They had shown feasibility and non-inferiority time to recurrence rate in MIS application. Morton *et al*. [34] concluded that MIS for IDS + HIPEC is a non-inferior option to the open technique with reduced recovery time, similar surgical time, and perioperative complication rates. MIS is also associated with a shorter interval to chemotherapy. One of the limitations of this trial is the small sample size and the lack of randomization because the surgical technique was chosen by the gynecological oncologist at the time of surgery and the patients submitted to MIS were generally with a lower tumor burden and lower surgical complexity [34,35].

4. Conclusions

The HIPEC option should be offered to patients with AOC eligible for IDS after neoadjuvant chemotherapy, since this treatment combination is shown to increase OS and DFS. Pharmacodynamic studies confirm that HIPEC achieves high concentrations of chemo agents in the abdominal cavity without increasing systemic toxicity.

It should not be missed that the application of HIPEC and the chance to obtain good outcomes for patients in terms of OS and DFS is conditioned by performing the treatment in an adequate surgical setting, with a team of gynecological oncologists able to ensure the best surgical outcome.

After a collaborative international work, a list of ten quality indicators was developed by the European Society of Gynecologic Oncology (ESGO) published in 2016 [36] and updated in 2020 [37], to identify appropriate centers for the treatment of AOC. This improves and standardizes the quality of care for patients and is an incentive to refer patients with AOC to specialized centers.

Author Contributions

GV, SR, SC, ABud, CA, EP, EMP and LD designed the research study. JM, AP, CVA, DA, ABuz and DC performed the research. SR provided help and advice on JM analyzed the data. GV, SR and JM wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. SC is serving as one of the Editorial Board members/Guest editors of this journal. We declare that SC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to SAF.

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