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Review

Hyperthermic Intraperitoneal Chemotherapy in the Management of Primary Epithelial Ovarian Cancer: A Debated Issue for Gynecologic Oncologists

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Abstract. *Hyperthermic intraperitoneal chemotherapy (HIPEC) has been widely investigated in patients with peritoneal carcinomatosis, including those with epithelial ovarian cancer (EOC), with conflicting results. The hyperthermia enhances drug tissue penetration, synergizes with several cytotoxic drugs including cisplatin, degrades BRCA2, suppresses homologous recombination, and elicits an anticancer immune response. A meta-analysis of retrospective studies including both patients with primary advanced EOC and those with recurrent platinum-sensitive EOC failed to detect a benefit in terms of progression-free survival (PFS) or overall survival (OS) from the addition of HIPEC after surgery. The aim of the present review was to analyze the recent randomized clinical trials designed to assess the value of HIPEC in the management of patients with primary advanced EOC. Although not free from criticism and bias, the available data from two phase III trials seem to suggest that the addition of HIPEC to interval debulking surgery after neoadjuvant chemotherapy significantly improves PFS and OS. Conversely, HIPEC does not appear to offer any advantage after primary debulking surgery. Several phase III trials are currently ongoing on these issues and the use of HIPEC is still a matter of debate in the scientific community. Additional translational research is strongly warranted to detect biological variables able to identify a subset of patients who may have a major benefit from this therapeutic approach. In particular, the clinical outcome of patients who undergo HIPEC should be correlated with BRCA status and homologous recombination repair status.*

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In the last decades hyperthermic intraperitoneal chemotherapy (HIPEC), consisting of induction of hyperthermia and delivery of chemotherapy into the peritoneal cavity after the completion of cytoreductive surgery, has been widely investigated in patients with peritoneal carcinomatosis including those with primary epithelial ovarian cancer (EOC) (1-18).

Chemotherapeutic drugs diluted in 0.9% normal saline are perfused in the abdominal cavity for 90 min at a target temperature ranging from 40˚C to 43˚C, through a specially designed pump, along with blanket cooling, intravenous (*iv.*) cold fluid hydration and ice pack application over the head. The hyperthermia enhances drug tissue penetration, acts synergistically with the commonly used cytotoxic agents such as cisplatin (CDDP), paclitaxel (PTX), oxaliplatin, and mitomycin, and increases CDDP-DNA adduct formation in tumor cells (4, 6, 19, 20). *In vitro* studies have shown that hyperthermia degrades $BRCA_2$, suppresses homologous recombination repair mechanisms and increases chemotherapy-induced tumor cell death (21). Moreover, HIPEC elicits an anticancer immune response through the exposure of cell surface heat shock proteins, enhancement of tumor cell chemokine production and activation of dendritic cells, cytotoxic T cells and natural killer cells (17, 22-24). HIPEC can be performed with either open or close technique. As far as the open technique is concerned, after the placement of inflow and drainage tubes through separate wounds as well

as of temperature sensors in the inflow system, in small pelvis and in diaphragmatic region, the skin surrounding the laparotomy is pulled toward the retractor placed above the anterior abdominal surface (4). The wound and retractor are covered with a plastic bag to prevent spillage of the perfusate and heat loss, and the surgeon can directly control the distribution of perfusate throughout the peritoneal cavity and can eventually stir bowel loops. After the end of HIPEC, the drainage tubes empty the abdominal cavity as much as possible. As for the close technique, inflow and outflow tubes and temperature sensors are placed in the pelvic cavity and in the sub-diaphragmatic spaces respectively, and the skin of the abdominal wall is closed with a temporary suture (8, 18). The patients are gently shaken from side to side to enhance the distribution of the chemotherapeutic agent within the peritoneal cavity. At the completion of HIPEC, the skin suture is removed, and the abdominal wall is closed layer by layer. With both open and close technique *iv.* sodium thiosulfate is usually administered as a bolus of 4-9 g/m^2 before HIPEC and then as a continuous infusion of 12 g/m^2 over 6 h to prevent CDDP-induced nephrotoxicity (4, 18). The patients are usually monitored in intensive care unit until stable.

Chiva and Gonzalez-Martin reviewed the retrospective data from 11 studies including 248 patients with advanced EOC and 8 studies including 499 patients with recurrent platinum-sensitive EOC, regarding the use of HIPEC in these clinical settings (2). Among patients with primary EOC who underwent primary debulking surgery (PDS) and HIPEC, median progression-free survival (PFS) was 14.4 months, median overall survival (OS) was 37.3 months, and 5-year OS rate was 40%. Among patients with recurrent disease, median PFS and median OS after HIPEC were 20.2 months and 36.5 months, respectively. Albeit with the limitations deriving from the retrospective design of the studies and from the heterogeneity of the criteria of patient selection, of the chemotherapeutic agents used and of the methods and times of administration, the authors failed to show any apparent advantage of HIPEC in terms of clinical outcome.

In this review we assessed the available data from randomized phase III trials as well as ongoing phase III trials on the use of HIPEC in the primary treatment of advanced EOC.

Hyperthermic Intraperitoneal Chemotherapy in Primary Advanced Epithelial Ovarian Cancer: Published Randomized Phase III Trials

Two randomized phase III trials have been recently published on the use of HIPEC in the treatment of patients with primary advanced EOC (4, 18) (Table I).

In the NCT00426257 trial 245 patients with FIGO stage III EOC, who had an objective response or a stable disease after three cycles of neoadjuvant chemotherapy (NACT) with *iv.* carboplatin (CBDCA) at the dose of area under curve (AUC) of 5 mg/ml/min (AUC5) + PTX 175 mg/m^2 every 3 weeks, were randomly allocated to receive interval debulking surgery (IDS) without or with HIPEC with CDDP 100 mg/m^2 at an intra-abdominal temperature of 40˚C for 90 min (4). HIPEC was performed with an open technique, and *iv.* sodium thiosulfate was administered as bolus at the dose of 9 g/m^2 at the start of HIPEC and then as continuous infusion of 12 g/m^2 over 6 h. Three additional cycles of the *iv.* PTX + CBDCA were given after surgery. The primary end-point of the study was PFS. After a median follow-up of 4.7 years, the risk of recurrence or death was 81% in the patients who received HIPEC compared to 89% in those who did not and the corresponding median PFS was 14.2 months and 10.7 months, respectively (p=0.003). The risk of death was 50% in the former *versus* 62% in the latter, and the corresponding median OS was 45.7 months and 33.9 months, respectively (p=0.02). Subgroup analyses revealed that HIPEC improved both PFS and OS regardless of patient age, histological type, and number of involved regions in the abdominal cavity. The incidence of grade 3-4 adverse events, mainly consisting of abdominal pain, infection, and ileus, was similar in the two arms (27% for HIPEC *versus* 25% for no-HIPEC, p=0.76). Twenty-nine patients who received HIPEC and 30 patients who did not underwent bowel resection, and a colostomy or ileostomy was performed in 21 of the former (72%) *versus* 13 of the latter (43%) (p=0.04). Since there is no evidence that HIPEC itself increases the risk of anastomotic leakage, this difference in the ostomy rate could reflect the surgeons' preference. The median interval time between IDS and the start of post-surgical chemotherapy was similar in the two groups (33 and 30 days, respectively). However, this study has been criticized for several reasons, such as the reduction of number of randomized patients because of slow accrual, the lower survival rates in both arms than expected, the heterogeneity of the results among the different centers, the unclear inclusion criteria for NACT, the probably underreported toxicity, especially for acute kidney injury, and the lack of stratification for relevant prognostic variables including BRCA status, histological type, FIGO substage and response rates to NACT (25-28).

Moreover, since all stage IV patients were excluded and most stage III patients might have been primarily cytoreduced to <1 cm residual disease, only a small group of patients with advanced disease fulfilled the inclusion criteria, which could not allow to extrapolate these results to all patients with advanced EOC.

In the NCT01091636 trial, 184 patients with FIGO stage III-IV EOC and <1 cm residual disease after either PDS (n.107) or IDS (n.77) were randomized to either HIPEC arm with CDDP 75 mg/m^2 or control arm (18). HIPEC was performed with a closed technique at target temperature of 41.5˚C for 90 min. *Iv.* sodium thiosulfate was not employed in the first 71 cases, whereas it was administered in the remaining 21 patients at the dose of 4 g/m^2 as a bolus before starting HIPEC and at the dose of 12 g/m^2 over 6 h during and after HIPEC. The

Table I. *Randomized clinical trials on hyperthermic intraperitoneal chemotherapy during primary debulking surgery or interval debulking surgery in patients with advanced epithelial ovarian cancer.*

Trial		Patients n.	Median PFS (months)	Median OS
NCT00426257 (4)	IDS + HIPEC	122	14.2	45.7
	IDS	123	10.7	33.9
	HR (95%CI)		0.66 (0.50-0.87)	0.67 (0.48-0.94)
NCT01091636 (18)	PDS/IDS + HIPEC	92	19.8	69.5
	PDS/IDS	92	18.8	61.3
	HR (95%CI)		0.88 (0.63-1.21)	0.87 (0.58-1.32)
	PDS + HIPEC	58	23.9	71.3
	PDS	49	29.7	NR
	HR (95%CI)		1.16 (0.74-1.83)	1.38 (0.75-2.54)
	IDS + HIPEC	34	17.4	61.8
	IDS	43	15.4	48.2
	HR (95%CI)		0.60 (0.37-0.99)	0.53 (0.29-0.96)

PFS: Progression-free survival; OS: overall survival; n.: number; IDS: interval debulking surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; 95%CI: 95% confidence Interval; PDS: primary debulking surgery.

performance of an ostomy after bowel surgery was similar in the two groups. The interval time between surgery and the start of subsequent chemotherapy was 22 days for the HIPEC arm and 20 days for the control arm. In the whole series, median PFS was 19.8 months in the patients who underwent HIPEC *versus* 18.8 months in those who did not (p=0.43), and the corresponding median OS was 69.5 months and 61.3 months (p=0.52), respectively. According to the timing of surgery, among the patients who underwent PDS median PFS and median OS were not significantly different between the two arms (p=0.51 and p=0.29, respectively). Conversely, among the patients treated with NACT and IDS both median PFS and OS were significantly better in the HIPEC arm compared with no-HIPEC arm (p=0.04 and p=0.04, respectively). Grade 3-4 adverse events occurred in 93.5% of the patients who received HIPEC and in 87.0% of those who did not, but no HIPEC-related death occurred. Increased prothrombin time (81.5% *versus* 65.2%, p=0.01), severe electrolyte alterations (80.4% *versus* 44.6%, p<0.001) and acute kidney injury (20.7% *versus* 6.5%, p=0.005) were more frequent in the HIPEC arm. The authors stated that a better control of intraperitoneal disease with the addition of HIPEC to IDS could be useful also in patients with stage IV EOC, since hyperthermia might stimulate antitumor immune responses.

Hyperthermic Intraperitoneal Chemotherapy in Primary Advanced Epithelial Ovarian Cancer: Ongoing Randomized Phase III Trials

Several phase III trials on HIPEC in primary EOC are currently ongoing (Table II). For example, the NCT03772028 (OVHIPEC-)2 trial has been planned to randomize 538 FIGO stage III EOC patients with no macroscopic residual disease or ≤2.5 mm residual disease after PDS to receive either HIPEC with CDDP 100 mg/m^2 for 90 min or no HIPEC. HIPEC is performed with open or closed technique with a target temperature of 40-41˚C. *Iv.* sodium thiosulfate is given at the start of perfusion and then is continued up until 6 h. All the patients receive six cycles of *iv.* platinum-PTX chemotherapy, followed by maintenance treatment with PARP-inhibitor (PARP-i) or bevacizumab in agreement with local guidelines (29). Pre-specified subgroup analysis will be performed for high-grade serous ovarian carcinoma *versus* other histological types as well as for somatic and germline mutated *BRCA versus* wild-type *BRCA*.

The NCT03842982 trial evaluates the use of HIPEC with CDDP 100 mg/m^2 heated to 40˚C for 90 min, along with *iv.* sodium thiosulfate, coupled with either PDS or IDS in 362 EOC patients. The study includes two exploratory objectives: the evaluation of the impact of HIPEC on the count of residual viable cells assessed by flow cytometry in abdominal drainage fluids and the creation of a biobank of tumor tissue samples and blood samples.

The NCT04280185 trial randomizes patients with stage IIc-IV EOC after PDS to either control arm or experimental arm. Patients of the control arm receive *iv.* PTX 175 mg/m^2 + CBDCA AUC 5-6 every 3 weeks for 6 cycles. In the patients enrolled in the experimental arm, HIPEC starts immediately after surgery, and it consists of intraperitoneal (*ip.*) PTX 60 mg/m^2 at the temperature of 43˚C for 60 min. A second HIPEC, performed 7 days later, uses *ip*. CBDCA AUC 5-6 at 43˚C for 30 min before PTX. On the 8th day, the patients receive *iv.* PTX 135 mg/m^2. After 3 weeks, 5 cycles of *iv.* chemotherapy with PTX + CBDCA are administered NCT03373058 is a randomized trial comparing HIPEC with docetaxel 75 mg/m^2 and CDDP 75 mg/m^2 in succession at

Table II. *Ongoing randomized clinical trials on hyperthermic intraperitoneal chemotherapy during primary debulking surgery or interval debulking surgery in patients with advanced epithelial ovarian cancer.*

Trial	Primary endpoint	Estimated study end date
NCT03772028 Phase III RTC for Stage III EOC randomizing Between PDS with or without HIPEC	OS	April 1, 2026
NCT03842982 Phase III RCT evaluating HIPEC in EOC considering two different settings: PDS and IDS	PFS	August 1, 2028
NCT04280185: Multicenter prospective RCT of HIPEC in the treatment of Stage IIc-IV EOC after PDS	PFS	May 1, 2024
NCT03373058: A phase III multicenter prospective RCT of HIPEC in the treatment of advanced-stage EOC after cytoreductive surgery	PFS	July 1, 2023
NCT03371693: A Phase III clinical trial of cytoreductive surgery plus HIPEC with lobaplatin in advanced and recurrent EOC	OS	March 30, 2023

RTC: Randomized clinical trial; EOC: epithelial ovarian cancer; OS: overall survival; HIPEC: hyperthermic intraperitoneal chemotherapy; PFS: progression-free survival; PDS: primary debulking surgery; IDS: interval debulking surgery.

43˚C for 90 min *versus* no HIPEC in patients with FIGO stage III EOC with residual disease <1 cm after PDS.

In the NCT03371693 trial patients with advanced or recurrent EOC are randomized to receive either HIPEC with lobaplatin 30 mg/m^2 at 41-43˚C for 60 min or no HIPEC after cytoreductive surgery. In the experimental arm, HIPEC is repeated at the 3rd and 5th day after surgery.

Hyperthermic Intraperitoneal Chemotherapy and *BRCA* Status in Epithelial Ovarian Cancer

Very few data are currently available as for a possible correlation between clinical outcome after HIPEC and *BRCA* status in patients with EOC. Safra *et al*. (30) noted a better median PFS in 27 patients with recurrent EOC who underwent complete surgical cytoreduction and HIPEC than in 84 matched patients with recurrent EOC who received chemotherapy alone (15 months *versus* 6 months, p=0.001). PFS was significantly longer in *BRCA* mutation carriers treated with cytoreductive surgery and HIPEC compared to *BRCA* mutation carriers treated with chemotherapy alone (20.9 *versus* 12.6 months, p=0.048). A retrospective, case-controlI Italian study compared 35 FIGO stage ≥ IIIb EOC patients previously treated with HIPEC after PDS within a phase II trial with a group of 35 patients matched for clinical and surgical characteristics who underwent PDS without HIPEC (31). There was no difference in PFS and OS between the two groups. It is noteworthy that among patients who did not receive HIPEC, PFS and OS were significantly better in mutated-*BRCA* compared to wild-type *BRCA* patients (p=0.011 and p=0.003, respectively), whereas among patients who underwent HIPEC, PFS and OS did not correlate with *BRCA* status (p=0.857 and p=0.372; respectively). This study would seem to suggest that HIPEC is beneficial especially in non-mutated *BRCA* patients, in whom it could improve their less favorable prognosis compared to mutated *BRCA* patients.

Conclusion

PDS followed by PTX/CBDCA - based chemotherapy is the standard therapeutic approach for advanced EOC whenever an optimal surgical resection seems to be achievable taking into account both disease spread and patient general conditions (28, 32, 33). Patients not fit for PDS undergo PTX/CBDCA-based NACT followed by IDS and additional chemotherapy with the same regimen. The introduction of bevacizumab and PARP-i in the first-line treatment of advanced EOC has significantly improved patient outcome (28, 33, 34).

Several studies and a Cochrane meta-analysis appeared to suggest that a first-line chemotherapy with an *ip*. component improved PFS and OS of patients with minimal residual disease after surgery (35). In the GOG 172 trial, 429 FIGO stage III EOC patients with residual disease ≤1 cm were randomly allocated to receive *iv*. PTX 135 mg/m^2 24-h infusion followed by either *iv*. 75 mg/m^2 CDDP on day 2 (*iv*. arm) or *ip*. 100 mg/m^2 CDDP on day 2 and *ip*. PTX 60 mg/m^2 on day 8 (*ip*. arm) every three weeks for 6 cycles (36). Only 42% of patients enrolled in the *ip*. arm completed all 6 cycles. However, an update of the study with a median follow-up of 10.7 years reported a median OS of 61.8 months for the *ip*. arm *versus* 51.4 months for the *iv*. arm [hazard ratio (HR) of death=0.77, 95% confidence interval (CI)=0.65-0.90] (37). There are some data suggesting that women with mutated BRCA may derive the greatest benefit from *ip*. therapy, probably for the more intensive and prolonged platinum exposure obtained by the *ip*. route in patients with defective double-strand break repair mechanisms (38-40). An immunohistochemical study performed on primary

tumor sections from patients enrolled in the GOG 172 trial found that an aberrant BRCA1 expression was an independent favorable prognostic variable for OS in women treated with *ip*. therapy (HR=0.67, 95%CI=0.47-0.97, p=0.032) (38). Conversely, no significant difference in OS was observed between the *ip*. and *iv*. arms in patients with normal BRCA1 expression. The GOG 252 trial randomized 1,560 patients to undergo 6 cycles of *iv*. PTX 80 mg/m^2 /week + *iv*. CBDCA AUC 6 on day 1 every three weeks or 6 cycles of *iv*. PTX 80 mg/m^2 /week + *ip*. CBDCA AUC 6 on day 1 every three weeks or 6 cycles of *iv*. PTX 135 mg/m^2 3-h infusion on day 1+ *ip*. CDDP 75 mg/m^2 on day 2 + *ip*. PTX 60 mg/m^2 on day 8 every 3 weeks (41). All arms received bevacizumab 15 mg/kg *iv*. on day 1 in cycles 2 to 22. There was no significant difference in PFS between the *iv*. regimen and either of the two *ip*. regimens. Therefore, when combined with bevacizumab, none of the two regimens with an *ip*. component improved the clinical outcome compared with *iv*. chemotherapy. Moreover, *ip*. chemotherapy is not free from specific drawbacks and adverse events, such as catheter-related complications, skin infections, bowel perforation, abdominal pain and infections and a higher incidence of severe fatigue or hematologic, gastrointestinal, metabolic, and neurologic toxicity (28, 35, 36, 42).

HIPEC as a single administration of *ip*. chemotherapy during surgery can overcome the catheter-related complications and inconveniences of serial *ip*. chemotherapy administrations, besides the potential benefits offered by the addition of hyperthermia to chemotherapy (4, 6). Another potential advantage of HIPEC is that it ensures that the whole peritoneal surface is wetted by the saline solution containing the chemotherapeutic agent before post-surgical adhesions develop (2, 6).

Although not free from criticism and bias, the available data from two randomized phase III trials seem to suggest a benefit in terms of PFS and OS from the addition of HIPEC to IDS after NACT in patients with primary advanced EOC (4, 18). However, the use of HIPEC is still a matter of debate in the scientific community. NCCN Guidelines take into consideration the HIPEC as on option at the time of IDS for all the patients with FIGO stage III EOC who have objective response or stable disease following three cycles of NACT, whereas this approach is not recommended after PDS (32).

According to the French clinical practice guidelines issued by FRANCOGYN, CNGOF, SFOG, and GINECO-ARCAGY, and endorsed by INCa, HIPEC can be proposed to patients with FIGO stage III EOC after complete cytoreduction at IDS (43).

ESMO/ESGO guidelines report that HIPEC is not a standard of care in the first-line treatment of EOC, with a level of evidence of II and a strength of recommendation of A, and that this approach should be reserved to patients enrolled in well-designed, prospective randomized clinical trials (28).

Additional translational research is strongly warranted to detect biological variables able to identify a subset of patients who may have a major benefit from this therapeutic approach. In particular the clinical outcome of patients who undergo HIPEC should be correlated with *BRCA* status and homologous recombination repair status. It is very interesting the prospective cohort study NCT05265117. This study assesses HIPEC in patients who have FIGO stage III-IV high-grade serous EOC, *BRCA* wild-type, homologous recombination repair defect and residual disease after PDS or IDS and who are eligible to the maintenance therapy with olaparib plus bevacizumab. As previously reported, the NCT03842982 trial involves the creation of a biobank for future translational investigations.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, A.G.; data curation, A.G.; writing – original draft preparation A.G.; writing – review and editing: A.G., S. C, and V.P.L. All Authors have read and agreed to the published version of the article.

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