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BRIEF ARTICLE

Cytoreductive surgery and HIPEC after neoadjuvant chemotherapy for advanced epithelial ovarian cancer

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Abstract

AIM: To reduce postoperative complications and to make possible an optimal cytoreduction, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery has been applied with encouraging results.

METHODS: Between December 2009 and February 2012, patients with stage ⅢC-Ⅳ epithelial ovarian cancer (EOC) underwent diagnostic laparoscopy, to assess the feasibility of optimal debulking surgery. The modified Fagotti score was applied to assess the feasibility of resection with zero residual tumor. Patients who were not candidate for upfront debulking surgery were submitted to NACT, then reassessed according to the RECIST 1.1 criteria and submitted to cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) if they showed clinical response or stable disease. The remaining cycles of adjuvant systemic chemotherapy (ASCT) were administered postoperatively, to complete 6 cycles of systemic chemotherapy.

RESULTS: Nine patients were included. Clinical response to NACT was complete in 3 patients and partial in 5 patients; one patient had stable disease. All patients underwent CRS resulting in CC0 disease prior to HIPEC. Average operative time was 510 min. Average intensive care unit stay was 2 d. Average postoperative hospital stay was 25 d. No postoperative mortality was observed. One patient experienced pelvic abscess. One patient refused ASCT. The remaining 8 patients started ASCT. Average time to chemotherapy was 36 d. All patients are alive, with an average follow up of 11 mo. Eight patients are disease-free at follow up.

CONCLUSION: HIPEC after CRS for advanced EOC is feasible with acceptable morbidity and mortality. NACT may increase the chance for achieving complete cytoreduction. Phase 3 studies are needed to determine the effects of HIPEC on survival.

Key words: Peritoneal carcinomatosis; Ovarian cancer; Cytoreductive surgery; Intraperitoneal chemotherapy; Hyperthermic intraperitoneal chemotherapy; Hyperthermia

Core tip: This is a report of a phase 2 prospective observational study, which served as a pilot study for the CHORINE trial protocol (http://www.chorine.org). Our pilot study supports the feasibility of neoadjuvant chemotherapy (NACT) followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for upfront treatment of advanced epithelial ovarian cancer. This combined therapy does not reduce the possibility to start the postoperative systemic chemotherapy in an acceptable period of time. We believe that in the upfront setting NACT can better select chemoresponsive patients, increasing their chance to take advantage from HIPEC, reducing the surgical stress and the perioperative complications.

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INTRODUCTION

Ovarian cancer is the third commonest gynecological neoplasm[1] and accounts for 5% of all female cancer deaths. Epithelial ovarian cancer (EOC) accounts for more than 70% of all ovarian cancers. EOC typically presents with unclear gastrointestinal and constitutional symptoms, like abdominal bloating, distension, weight loss, and fatigue[2]. Due to heterogeneity of these symptoms, nearly 70% of patients with EOC are diagnosed with advanced stage disease (stage Ⅲ or Ⅳ)[3,4].

It is well known that primary cytoreductive surgery (CRS) followed by platinum-based systemic adjuvant chemotherapy (SACT), when indicated, is the mainstay of treatment for EOC: in this setting, the aim of primary surgery is to remove as much tumor as possible (possibly all the tumor), since the amount of residual tumor is one of the most important prognostic factors for survival[5-7]. Unfortunately, the achievement of optimal cytoreduction (residual tumor less than 1-2 cm), mainly in advanced EOC, is not always possible, due to the amount of disease at presentation, patient's co-morbidities, and the experience of the surgeon[8-11]. Not performing optimal or complete CRS results in loosing the chance for longer survival.

To help achieving complete resection rate, the concept of neoadjuvant chemotherapy (NACT) followed by interval CRS (ICRS) has been developed for patients deemed to have unresectable disease (stage ⅢC/Ⅳ EOC). From several retrospective and prospective case-control studies, along with recent meta-analyses, it appears that NACT-ICRS compared to primary CRS offers less postoperative morbidity to patients[12]. Moreover, results of the prospective randomized controlled trial (RCT) EORTC 55971 are consistent with the majority of the previous studies, suggesting that NACT-ICRS results in the same survival but fewer complications than primary CRS in patients with stage ⅢC/Ⅳ EOC[13].

During its natural history, EOC tends to be chemosensitive and to confine itself to the surface of the peritoneal cavity for a long period of time. These features make it an obvious target for intraperitoneal chemotherapy (IPCT), which is given by infusion of the chemotherapeutic agents directly into the peritoneal cavity. This may increase the anticancer effect with fewer systemic adverse effects in comparison to intravenous therapy. To optimize drug distribution, IPCT has also been applied intraoperatively, immediately after CRS. Different techniques have been used for intraoperative IPCT. An advantage of intraoperative use is that IPCT can be administered even under hyperthermic conditions, which are poorly tolerated by a patient who is awake. Hyperthermia is directly cytotoxic and enhances the efficacy and penetration depth of many drugs, while the mild locoregional hyperthermia that is used has no significant adverse effects.

The feasibility of hyperthermic intraperitoneal chemotherapy (HIPEC), as a treatment for peritoneal carcinomatosis, was first demonstrated by Spratt *et al*[14]. Its development continued under Dr. Sugarbaker in the mid-1990s, who advocated a combined procedure of CRS with peritonectomy procedures (aimed at resecting peritoneal surfaces with tumor implants) and associated visceral dissections, with maximal surgical effort to remove as much tumor as macroscopically possible, followed by direct instillation of heated IPCT to address microscopic residual disease[15]. This treatment has already been shown to be beneficial for patients with peritoneal carcinomatosis from gastric cancer[16] appendiceal cancer[17], colorectal cancer[18] and peritoneal mesothelioma[19].

The rationale to use CRS and HIPEC in EOC stands on a few considerations. First, phase 3 RCTs have established the superiority (improved progression-free and overall survival) of intraperitoneal cisplatin-based chemotherapy compared to the systemic delivery of the agent in the treatment of small-volume residual advanced EOC[20-22]. Second, a number of prospective phase 2 studies and retrospective institutional experiences have shown the feasibility of employing HIPEC[23-28], when complete macroscopic cytoreduction is achieved prior to the delivery of the antineoplastic agents. However a few concerns still exist about the application of IPCT because of the fear of possible complication linked to this way of chemotherapy administration. The prospected main risk is to delay or to definitively obstacle the possibility to start systemic chemotherapy as soon as possible after the surgery.

For these reasons we performed a bi-centric prospective observational pilot study combining NACT with carboplatin (CBCDA) and paclitaxel (PTX) to CRS and HIPEC with cisplatin (CDDP) and PTX in upfront treatment of advanced EOC. The aim of this study was to evaluate the feasibility of CRS and HIPEC in patients

with stage ⅢC/Ⅳ EOC, who showed partial or complete response after NACT, in terms of percentage of complete cytoreduction (residual disease < 2.5 mm), toxicity, postoperative complications, postoperative mortality, and time elapsed till the start of systemic chemotherapy (time to chemotherapy, TTC).

MATERIALS AND METHODS

The Study design was approved by our local Ethics Committee. The selection criteria were the following: (1) Inclusion criteria. Female adult women (18 to 70 years old) patients, with EOC (FIGO stage ⅢC or Ⅳ), performance status (ECOG) 0, 1 or 2, signed informed consent, body mass index < 35 kg/m^2; and (2) Exclusion criteria. Impossibility of an adequate follow-up, presence of other active neoplasms, active infection or other concurrent medical condition that could interfere in the ability of patients to receive the proposed treatment according to protocol, complete bowel obstruction, abnormal bone marrow indices or renal and liver function, ASA Ⅳ or Ⅴ.

Patients with advanced EOC (stage ⅢC-Ⅳ) were submitted to a diagnostic laparoscopy, to assess the feasibility of optimal debulking surgery with no residual disease at the end of the procedure.

Laparoscopy was performed by trained gynecologists and surgeons. In presence of ascitic fluid, a sample for cytology was obtained; otherwise, a lavage of the peritoneal cavity was performed; biopsy of eventual pelvic and peritoneal masses was obtained.

The modified Fagotti scoring system was applied[29], to assess the feasibility of resection with zero residual tumor. Patients with a score ≥ 4 were judged not candidate for debulking surgery: a score ≥ 4 was chosen as a compromise to warrant adequate accrual, because the higher risk of inappropriate lack of exploration (27.3%) was likely to be balanced by the documented efficacy of NACT in this type of tumor.

After laparoscopic evaluation, patients who were not candidate for upfront debulking surgery were submitted to NACT with CBCDA AUC-5 and PTX 175 mg/m^2, administered every 21 d.

After 3-6 cycles of chemotherapy, patients were re-assessed by clinical, radiologic [computed tomography (CT) scan] and laboratory (CA 125) evaluation and assigned to one of four subgroups, according to the RECIST 1.1 criteria: complete clinical response (cCR), partial clinical response (cPR), clinically stable disease (cSD), clinically disease progression (cDP)[30]. Patients with cCR, cPR or cSD after NACT, were submitted to CRS with radical intent.

After laparotomy, a detailed pattern of peritoneal diffusion of the disease was drawn according to the Peritoneal Cancer Index (PCI) scoring system[31] and then CRS was as follows: hysterectomy, bilateral salpingoophorectomy, pelvic and peri-aortic lymphadenectomy, radical omentectomy, random biopsy of peritoneal surfaces, associated to any surgical procedure needed to obtain a ≤ 2.5 mm residual tumor (peritonectomy, bowel resection, diaphragmatic stripping, gastric resection, *etc.*).

After CRS, patients with adequate cytoreduction (CC0, no residual disease; CC1, residual tumor ≤ 2.5 mm)[29] were submitted to HIPEC with CDDP (100 mg/m^2 of body surface area) and PTX (175 mg/m^2 of body surface area) at 42 ℃, with an intraperitoneal infusion time of 90 min. HIPEC was delivered using an open abdomen (coliseum) technique.

Toxicity was recorded in accordance to the National Cancer Institute Common Toxicity Criteria (NCI CTC). Surgical complications were considered as a component of the total toxicity and also registered in accordance of the NCI CTC. Treatment-related death was defined as death due to toxicity following cytoreduction and HIPEC without time interval restrictions.

As soon as the conditions of the patients allowed it (and in any case at least 4 wk after surgery) the remaining cycles of SACT were administered with the same schedule of NACT, to complete 6 cycles of systemic chemotherapy.

RESULTS

Between December 2009 and February 2012, 36 patients with advanced EOC (stage ⅢC-Ⅳ) were evaluated and submitted to a diagnostic laparoscopy: 15 patients were selected who were not candidate for upfront debulking surgery (13 stage ⅢC, 2 stage Ⅳ) and submitted to NACT with CBCDA AUC-5 and PTX 175 mg/m^2, administered every 21 d.

After three cycles of NACT, 6 patients were excluded for evidence of cDP; in the remaining 9 patients, cCR was observed in 3 cases, cPR was observed in 5 cases, one patient had cSD: these 9 patients were enrolled in our pilot study.

Six patients underwent CRS and HIPEC after four cycles of NACT, 2 patients after three cycles of NACT and 1 patient after six cycles of NACT, in order to achieve optimal clinical response (> 50%, according to the RECIST 1.1 criteria). Average age was 55.8 years (median 55 years, range 45-65 years).

At operation, average PCI was 14 (median 13, range 5-28). All patients underwent CRS resulting in CC0 disease prior to HIPEC. Supramesocolic compartment peritonectomy was required in 5 patients. Six patients underwent colorectal resection and anastomosis, with temporary diverting ileostomy. More clinical details are available in Table 1.

All patients underwent HIPEC with CDDP 100 mg/m^2 of body surface area and PTX 175 mg/m^2 of body surface area at 42 ℃, with an intraperitoneal infusion time of 90 min.

Average operative time was 510 min (median 520 min, range 400-595 min). Average intensive care unit stay was 2 d (median 2 d, range 1-5 d). Average postoperative hospital stay was 25 d (median 22 d, range 9-35 d).

No postoperative mortality was observed. One patient

Table 1 Clinical characteristics of the ovarian cancer patients

Patient	Age (yr)	BMI (kg/m^2)	Stage	Histology	Grade	PCI	No. of cycle NACT	Clinical response (%)	CC
1	47	23	IIIC	Sierous	3	15	4	100	0
2	50	31	IV	Sierous	3	12	4	> 50	0
3	53	31	IV	Endometrioid	3	6	4	100	0
4	65	19	IIIC	Sierous	2	8	4	> 50	0
5	55	24	IIIC	Sierous	3	21	4	100	0
6	55	21	IIIC	Undifferentiated	3	28	4	< 50	0
7	47	22	IIIC	Endometrioid	3	5	3	> 50	0
8	62	22.9	IIIC	Sierous	3	14	6	> 50	0
9	65	20	IIIC	Sierous	3	13	3	> 50	0

BMI: Body mass index; PCI: Peritoneal cancer index; NACT: Neoadjuvant chemotherapy.

Table 2 Postoperative adverse events *n* (%)

	Patients	CTCAE grade	Treatment
Postoperative death	0 (0)		
Reoperation	1 (11)		
Types of complications	5 (56)		
Grade 3-5 morbidity	5 (56)		
Pelvic abscess	1 (11)	3	Reoperation
Leukopenia	3 (33)	3	G-CSF
Thrombocytopenia	2 (22)	3	Observation

G-CSF: Granulocyte colony-stimulating factor.

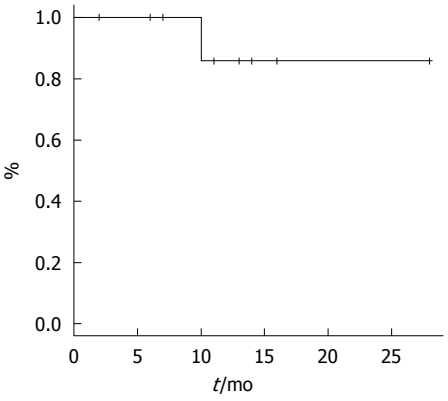

Figure 1 Disease free survival curve.

experienced a grade 3 postoperative complication (pelvic abscess), requiring reoperative debridement and drainage. Grade 3 leukopenia was observed in 3 patients and was treated with administration of granulocyte colony-stimulating factor; one of these patients had also grade 3 thrombocytopenia. One more patient experienced Grade 3 thrombocytopenia, which resolved spontaneously (Table 2).

One patient refused SACT. The remaining 8 patients started SACT. Average TTC was 36 d (median 29 d, range 25-62 d). All patients are alive, with an average follow up of 12 mo (median 11 mo, range 2-28 mo). Eight patients are disease-free to date. One patient showed a raising CA 125 after 10 mo of follow up. The disease-free survival curve for the 9 patients included in the study is shown in Figure 1.

DISCUSSION

In our presented study, 36 women with advanced EOC were evaluated by means of laparoscopy and 15 of them (41.6%) were judged not suitable for optimal CRS, adopting the modified Fagotti score with a cut-off of 4. These 15 patients were treated with NACT, and then 9 of them (those with cCR, cPR or cSD) underwent CRS and HIPEC with complete cytoreduction (CC0), few postoperative complications and no mortality. All patients but one, who refused it, were able start SACT in an average time of 36 d after CRS + HIPEC. All of them were able to complete SACT after CRS and HIPEC. Eight out of 9 patients are disease free to date and all of them are alive after a median follow up of 11 mo.

Even if the number of patients enrolled is small, our study shows that performing CRS and HIPEC after NACT was safe and led to a 100% rate of optimal cytoreduction, in patients with advanced EOC previously judged not suitable for complete cytoreduction at diagnostic laparoscopy. Except for the patient who refused postoperative SACT, all of the patients were able to complete SACT after CRS and HIPEC, with an acceptable TTC.

The strategy adopted in our study is not the recognized standard treatment of advanced EOC, namely maximal CRS followed by platinum-based SACT: nevertheless, patients are selected for this strategy only if they are judged not suitable for complete CRS by means of laparoscopy and a recognized scoring system[29]. Those patients are offered CRS after NACT and HIPEC is added to address microscopic residual disease: our study shows that this strategy is feasible, safe and does not flaw the completion of systemic CT.

Follow up is short, but preliminary results are encouraging and comparable to those achieved in other phase 2 studies available in the literature.

A recent article by Deraco *et al*[32] reported the results of a multi-center phase 2 trial using CRS and closed-abdomen HIPEC with CDDP and doxorubicin, in front-line treatment of advanced EOC. The authors accrued 26 patients over 6 years in four different Italian centers, achieving macroscopically complete cytoreduction in 15

Table 3 Studies on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in upfront setting

Ref.	Patients (neoadjuvant)	Type of NACT	HIPEC (technique, drug and dose, temperature, lenght of infusion time)	Period	Country
Steller *et al*[46]	2		C, carboplatin 800-1200 mg/m^2, 41-43 ℃, 90 min	NR	United States
Look *et al*[44]	4		O, doxorubicin, NR, NR	1988-2001	Singapore
Piso *et al*[45]	8 (1)	*iv* TPB	O, cisplatin 75 mg/m^2, NR, 90 min	1995-1999	Germany
Reichman *et al*[43]	9 (9)	*iv* PB	O, cisplatin 50 mg/m^2, 40 ℃, 90 min	2001-2004	United States
Rufián *et al*[42]	19		O, paclitaxel 60 mg/m^2, 41-43 ℃, 60 min	1997-2004	Spain
Roviello *et al*[47]	45 (31)	*iv* TPB	C, mitomycin C 25 mg/m^2 + cisplatin 100 mg/m^2, 41-43 ℃, 60 min	2000-2009	Italy
Pavlov *et al*[39]	31		C, doxorubicin 0.1 mg/kg (+ EPIC 15 mg/m^2 × 5 d), NR, NR	1995-2007	Serbia
Guardiola *et al*[40]	31 (31)	*iv* TPB	O, cisplatin 180 mg, 37 ℃, 120min	2003-2006	France
Di Giorgio *et al*[41]	22 (4)	*iv* TPB	C, cisplatin 75 mg/m^2, 42-43 ℃, 60 min	2000-2007	Italy
Lim *et al*[48]	30 (14)	NR	C, cisplatin 75 mg/m^2, 41.5 ℃, 90 min	2007-2009	Korea
Frenel *et al*[49]	7 (7)	*iv* TPB	O, oxaliplatin, 360-460 mg/m^2, 41-43 ℃, 30 min	2005-2008	France
Muñoz-Casares *et al*[50]	10 (10)	*ip* TB (+ in 5 pts *iv* PB)	O, paclitaxel, 60 mg/m^2, 41-43 ℃, NR	2004-2009	Spain
Parson *et al*[38]	51		C, carboplatin 1000 mg +mitomycin C 30 mg, 41-42 ℃, 60-120 min	1996-2009	United States
Deraco *et al*[32]	26		C, cisplatin 40 mg/L of perfusate + doxorubicin 15 mg/L of perfusate), 42.5 ℃, 90 min	2004-2010	Italy

NACT: Neoadjuvant chemotherapy; O: Open method; C: Closed method; TPB: Taxanes and platinum based; PB: Platinum based; TB: Taxanes based; NR: Not reported; HIPEC: Hyperthermic intraperitoneal chemotherapy.

patients and only minimal residual disease (≤ 2.5 mm) in the remaining 11.

Four patients experienced major complications, including one postoperative death. 25 out of 26 patients started SACT after CRS + HIPEC, with a median TTC of 46 d. Five-year overall survival was 60.7% and progression-free survival was 15.2%. Although these results are encouraging, in absence of a phase 3 trial, before suggesting that CRS + HIPEC could be a valid strategy for upfront treatment of advanced EOC a few considerations should be done.

It is well known that CRS, especially in very advanced cases, is associated to a high incidence of postoperative morbidity and mortality[33-35] and that the HIPEC procedure could even increase the incidence of perioperative complications[36]. For these reasons, HIPEC should be considered a burdensome procedure and before performing it, every effort is needed to select which patients will achieve the maximum benefit from it.

Although the majority of patients with EOC (up to 80%) respond to first-line systemic platinum based chemotherapy, 20% of them are resistant or refractory[37]. According to these data, a certain percentage of women with chemoresistant tumor cells will not benefit from administration of high dose HIPEC after upfront CRS for advanced EOC.

Even if not detailed in the article by Deraco *et al*[32], the survival curve of the patients accrued in their phase 2 study shows that almost 30% of the patients recurred at 1 year. It is reasonable to suppose that these patients were not chemo-sensitive.

HIPEC should be active on chemosensitive cells and the procedure could be avoided in women with insensitive tumor cells. Even if NACT followed by CRS + HIPEC did not show better results in terms of PFS and OS[13], the evaluation of patients' response to NACT could be a strategy to select for HIPEC only the patients who show a chemo-sensitivity to platinum and taxanes.

There are some phase 2 observational studies[32,38-51] in the literature reporting a total of 295 patients with primary EOC treated with CRS and HIPEC in upfront setting, with an approach that is similar to the study of Deraco *et al* (Table 3).

All these phase 2 observational studies include patients where in most cases a great surgical effort has been made and the chemosensibility state was not known: in only 107 cases (36.3%) the patients had undergone NACT to test *in-vivo* chemosensitivity before CRS and HIPEC.

The idea of proposing NACT in patients with very advanced EOC and performing ICRS associated to HIPEC, like in our study, could have various advantages. First, NACT can select "*in vivo*" chemosensitive patients, thus making possible to offer the HIPEC procedure only to those patients that are highly responsive to the chemotherapeutic molecules. Second, NACT reduces the surgical load and consequently surgery obtains no residual tumor in the vast majority of this set of patients. Third, the less radical surgery required is associated to lesser perioperative complications, permitting shorter recovery to start with postoperative chemotherapy. And last, this strategy could be offered to an high proportion of women with advanced EOC[13,52].

In our study, 6 out of 15 women (40%) showed cDP after NACT: this percentage of non-responders to NACT is low compared to those of previous studies including EORTC trial[13]. Anyway, we should consider that the decision to adopt the RECIST criteria in our study was made to clearly select highly responsive patients. In fact, after CRS all women were CC0.

If we consider the EORTC study, 295 out of 334 women were submitted to CRS after NACT, and residual tumor < 1 cm was achieved in 80.6% of 295 women: this means that 97 out of 334 women assigned to NACT (30%) were non-responders. Moreover, it is reasonable to think that if a residual tumor < 2.5 mm (CC1) or no residual

tumor (CC0) was used in the EORTC trial to define optimal cytoreduction after CRS, a higher percentage of non-responders to NACT could have been found.

Although according to the results of our study, NACT could offer the opportunity to reduce the surgical load needed to achieve optimal cytoreduction and make possible to perform CRS and HIPEC with only minor complications and no postoperative mortality, many scientists agree that RCTs are needed to confirm the potential advantages of HIPEC associated to CRS in all time points of the natural history of advanced EOC, but especially in upfront setting[53-55]. Only RCTs will clarify the role of CRS and HIPEC in advanced EOC, as already has been done for colon and gastric cancer[56,57].

To our knowledge, regarding the use of CRS and HIPEC in advanced EOC, at least four RCTs are ongoing. The first study is a Korean RCT including primary and recurrent EOC[58]. Two different RCTs have been proposed by St George Hospital in Sydney (Australia), to test HIPEC in primary and recurrent EOC[59]. A third multicentric RCT (CHIPOR trial), testing HIPEC in recurrent EOC, has been planned by French surgeons[60]. The fourth RCT, conceived by the Netherlands Cancer Institute (OVHIPEC trial), evaluates the efficacy of secondary cytoreduction, with or without HIPEC, in patients with advanced EOC, eligible for interval debulking surgery either following primary chemotherapy or following incomplete primary debulking and chemotherapy. The experimental group undergoes interval debulking with HIPEC (CDDP 100 mg/m^2) at the end of CRS, while the control group is treated only with interval debulking surgery[61].

Similarly to the last described RCT, where HIPEC is used in upfront setting after primary chemotherapy, our groups have recently proposed the transformation of our above mentioned pilot study (following its philosophy) in a RCT called CHORINE Study (Cytoreduction and Hipec in the treatment of OvaRIaN cancEr). This study project is a multicentre phase 3 prospective RCT, comparing CRS and HIPEC (CDDP+PTX) *vs* CRS alone in stage ⅢC unresectable EOC with partial or complete response after 3 systemic cycles of CBCDA + PTX (NACT), followed by further 3 cycles of CBCDA + PTX (SACT). The choice to add PTX to CDDP in the HIPEC perfusate takes count of the negligible toxicity observed in our pilot study and the efficacy of PTX reported in the literature, where a significant increase in survival is observed when heated intraperitoneal PTX is administered after CRS[62-67]. In the CHORINE study the primary outcome is 2-year disease-free survival.

Only patients with complete or cPR after the 3 cycles of NACT will be eligible for the study and, after signing the informed consent form, will be submitted to CRS with radical intent. The randomization (HIPEC *vs* no HIPEC) will be applied during the surgical procedure after adequate CRS (residual tumor ≤ 2.5 mm): patients with suboptimal cytoreduction (residual tumor > 2.5 mm) are considered not suitable for randomization and will be excluded.

The drug schedule elected in the CHORINE study is CDDP 100 mg/m^2 of body surface area and PTX 175 mg/m^2 of body surface area with an intraperitoneal infusion time length of 90 min.

A sample size of 47 patients for each group has been calculated to reach a confidence level of 95% with a power of 80%, considering a 45% and 75% disease-free survival at 2 years of follow-up in non-HIPEC and HIPEC group respectively.

On the one hand the advantages of CHORINE study are the following: (1) NACT selects for inclusion in the study only patients in whom there is a clinical response (test of *in-vivo* chemosensitivity) and then a response to HIPEC is expected; (2) response to NACT should make the cytoreductive effort less demanding, increasing the occurrence of complete CRS and presumably lowering the morbidity; and (3) HIPEC is the only variable between groups in the study, making it possible to evaluate its effectiveness regardless of CRS, because a radical and complete cytoreduction is required either in the experimental arm than in the control group (as requested by many authors in the literature[53]).

On the other hand, the major limitation of the study is that the control group is not the recognized standard treatment for advanced EOC, namely maximal CRS followed by platinum-based SACT.

The CHORINE study has been approved by our review board and we are in the process to complete the administrative requirements and recruiting the other participating centers.

In conclusion, our pilot study supports the feasibility of NACT followed by CRS and HIPEC for upfront treatment of advanced EOC. This combined therapy does not reduce the possibility to start the post-operative systemic chemotherapy in an acceptable period of time. We believe that in the upfront setting NACT can better select chemoresponsive patients, reducing thus the surgical stress and the perioperative complications.

Based on the results of this pilot study, our proposed phase 3 trial (the CHORINE study) will clarify the relative benefits of HIPEC, that have been though to support the course of action of CRS by targeting microscopic residual tumoral intraperitoneal disease in advanced EOC.

COMMENTS

Background

Ovarian cancer is the third commonest gynecological neoplasm and accounts for 5% of all female cancer deaths. Epithelial ovarian cancer (EOC) accounts for more than 70% of all ovarian cancers. Primary cytoreductive surgery (CRS) followed by platinum-based systemic adjuvant chemotherapy (SACT), when indicated, is the mainstay of treatment: unfortunately, the achievement of optimal cytoreduction (residual tumor less than 1-2 cm), mainly in advanced EOC, is not always possible. To help achieving complete resection rate, the concept of neoadjuvant chemotherapy (NACT) followed by interval CRS has been developed for patients deemed to have unresectable disease (stage ⅢC/Ⅳ EOC). A number of prospective phase 2 studies and retrospective institutional experiences have shown the feasibility of employing hyperthermic intraperitoneal chemotherapy (HIPEC) when complete macroscopic cytoreduction is achieved; however a few concerns still exist. For these reasons the authors performed a bi-centric prospective observational pilot study combining NACT with carbo-

platin (CBCDA) and paclitaxel (PTX) to CRS and HIPEC with cisplatin (CDDP) and PTX in upfront treatment of advanced EOC. The aim of this study was to evaluate the feasibility of CRS and HIPEC in patients with stage ⅢC/Ⅳ EOC, who showed partial or complete response after NACT, in terms of percentage of complete cytoreduction (residual disease < 2.5 mm), toxicity, postoperative complications, postoperative mortality, and time elapsed till the start of systemic chemotherapy (time to chemotherapy, TTC).

Research frontiers

Based on the results of this pilot study, the authors developed the CHORINE study protocol (www.chorine.org), a multicentre phase 3 prospective RCT, comparing CRS and HIPEC (CDDP + PTX) *vs* CRS alone in stage ⅢC unresectable EOC with partial or complete response after 3 systemic cycles of CBCDA+PTX (NACT), followed by further 3 cycles of CBCDA + PTX (SACT). Only RCTs will clarify the role of CRS and HIPEC in advanced EOC, as already has been done for colon and gastric cancer.

Innovations and breakthroughs

The cornerstones of developing the CHORINE study protocol are the following: (1) NACT selects for inclusion in the study only patients in whom there is a clinical response (test of *in-vivo* chemosensitivity) and then a response to HIPEC is expected; (2) response to NACT should make the cytoreductive effort less demanding, increasing the occurrence of complete CRS and presumably lowering the morbidity; and (3) HIPEC is the only variable between groups in the study, making it possible to evaluate its effectiveness regardless of CRS, because a radical and complete cytoreduction is required either in the experimental arm than in the control group (as requested by many authors in the literature).

Applications

The study results suggest that NACT followed by CRS and HIPEC is a feasible strategy for upfront treatment of advanced EOC.

Terminology

CRS: the aim of surgery for advanced EOC is to remove as much tumor as possible, since the amount of residual tumor is one of the most important prognostic factors for survival. HIPEC: during its natural history, EOC tends to be chemosensitive and to confine itself to the surface of the peritoneal cavity for a long period of time. These features make it an obvious target for intraperitoneal chemotherapy (IPCT), which is given by infusion of the chemotherapeutic agents directly into the peritoneal cavity. This may increase the anticancer effect with fewer systemic adverse effects in comparison to intravenous therapy. To optimize drug distribution, IPCT has also been applied intraoperatively, immediately after CRS. An advantage of intraoperative use is that IPCT can be administered even under hyperthermic conditions, which are poorly tolerated by a patient who is awake. Hyperthermia is directly cytotoxic and enhances the efficacy and penetration depth of many drugs, while the mild locoregional hyperthermia that is used has no significant adverse effects.

Peer review

The authors presented preliminary results from a pilot study evaluating the feasibility and safety of HIPEC after NACT and CRS in 9 patients with advanced ovarian cancer. They showed that this strategy was feasible and safe and had acceptable TTC. The topic of HIPEC after CRS for advanced ovarian cancer is interesting and worth being evaluated in a large-scale clinical study.

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