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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: Multi-institutional phase-II trial

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ABSTRACT

Objective. The primary end-point of this multi-institutional phase-II trial was to assess results in terms of overall survival after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in treatment-naive epithelial ovarian cancer (EOC) with advanced peritoneal involvement. Secondary end-points were treatment morbi-mortality and outcome effects of time to subsequent adjuvant systemic chemotherapy (TTC).

Methods. Twenty-six women with stage III–IV EOC were prospectively enrolled in 4 Italian centers to undergo CRS and closed-abdomen HIPEC with cisplatin and doxorubicin. Then they received systemic chemotherapy with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles.

Results. Macroscopically complete cytoreduction was achieved in 15 patients; only minimal residual disease ($\leq$2.5 mm) remained in 11. Major complications occurred in four patients and postoperative death in one. After a median follow-up of 25 months, 5-year overall survival was 60.7% and 5-year progression-free survival 15.2% (median 30 months). Excluding operative death, all the patients underwent systemic chemotherapy at a median of 46 days from combined treatment (range: 29–75). The median number of cycles per patient was 6 (range: 1–8). The time to chemotherapy did not affect the OS or PFS.

Conclusions. In selected patients with advanced stage EOC, upfront CRS and HIPEC provided promising results in terms of outcome. Morbidity was comparable to aggressive cytoreduction without HIPEC. Postoperative recovery delayed the initiation of adjuvant systemic chemotherapy but not sufficiently to impact negatively on survival. These data warrant further evaluation in a randomized clinical trial.

Introduction

Epithelial ovarian cancer (EOC) is the ninth most common malignancy and fifth leading cause of cancer-related deaths among females in the USA [1]. In up to 75% of women, the disease is diagnosed at an advanced stage, with peritoneal involvement or distant metastases (International Federation of Gynecology and Obstetrics, FIGO stage III–IV) [2].

Primary surgical cytoreduction and combination chemotherapy represents the current treatment paradigm for advanced EOC [2]. Clinical studies have shown that intravenous carboplatin/taxol-based first-line chemotherapy achieves the highest response rate [3,4]. However, outcome results remain unsatisfactory with long-term survival rates of only 20–30%, since disease recurrences are common even after complete response to chemotherapy [3,4]. Second-line treatments can improve survival and quality of life but are not curative, and patients ultimately die of nonresponsive progressive disease [2]. Neoadjuvant chemotherapy (NACT) followed by surgery is a different approach which has not demonstrated better results in clinical trials [5,6]. Adjunctive treatments to reduce the risk for relapse after standard-of-care therapy, including extension of front-line agents, high-dose chemotherapy, whole-abdominal or intraperitoneal radiotherapy, immunotherapy, biological therapy and single-agent paclitaxel, have not shown any survival advantage in several phase-III trials [2,7].

Aggressive cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a comprehensive treatment approach directed at definitive disease eradication which has been successfully used in the management of peritoneal surface malignancies. It involves peritonectomy procedures and multivisceral resections to remove the macroscopic tumor, and HIPEC to treat the microscopic residual disease [8–11]. HIPEC combines the pharmacokinetic advantage

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of intracavitary chemotherapy delivery (i.e. regional dose intensification) with those of hyperthermia (i.e. selective malignant cell-killing effect and enhancement of the antiblastic effect and tumor tissue penetration of certain chemotherapies) [12].

For several reasons, there has been growing interest for this innovative treatment in the management of advanced EOC. First, the disease marked propensity for peritoneal spread, which makes it suitable for aggressive loco-regional therapies [13]. Second, retrospective analysis and a recent meta-analysis have repeatedly demonstrated that optimal resection of metastatic disease is one of the most powerful determinants of survival [14,15]. Third, the superiority of intraperitoneal versus systemic administration of chemotherapeutic agents has been shown in large randomized trials [16–18].

Despite the established rationale and encouraging results of several independent studies [19–24], a certain degree of scepticism still surrounds CRS and HIPEC [25]. Criticisms involve inherent potential morbidity and the lack of randomized data confirming its theoretical advantage. A major concern is that the longer postoperative convalescence time may result in delay, decreased dose-intensity or even withdrawal from the subsequent systemic chemotherapy, thus adversely affecting prognosis.

Therefore we conducted a multi-institutional phase-II trial to assess overall survival (OS) after upfront CRS and HIPEC as the first step of a comprehensive treatment plan for advanced EOC, involving both loco-regional and systemic therapies. Furthermore, the safety profile of combined treatment was assessed. The third end-point was to test whether the time elapsing from CRS and HIPEC to the initiation of systemic chemotherapy (time-to-chemotherapy—TTC) could have an impact on prognosis [26].

Patients and methods

This multi-institutional phase-II study was conducted in four Italian centers: the Milan National Cancer Institute, and the General Surgery Units of one university and two community hospitals. The accrual period encompassed from November 2004 to June 2010. The study was closed in July 2010. All the patients were treated according to a clinical protocol approved by the Institutional Ethics Committees of participating institutions and signed informed consent forms.

Eligibility criteria for combined treatment included: histological diagnosis of EOC; no previous systemic or intraperitoneal chemotherapy; no previous significant surgical cytoreduction; age ≤ 75; performance status ≤ 2 according to the Eastern Cooperative Oncology Group (ECOG) [27]; no significant co-morbidities; peritoneal disease amenable to complete surgical cytoreduction and no extra-abdominal or hepatic metastases at preoperative computed tomography $\pm$ fludeoxyglucose (FDG) positron emission tomography. Thirty patients were screened for the present trial. Four of them were excluded, due to lung metastases ($n=1$), massive small bowel mesentery involvement ($n=1$), and ECOG score >2 ($n=2$). They were given systemic chemotherapy ($n=2$) or support therapy ($n=2$). If a recruited patient resulted to be unresectable at laparotomy she was included in the analysis, according to intention to treat principle.

Operative treatment

Cytoreductive surgery was based on the technique originally described by Sugarbaker [28], with some modifications [29]. Briefly, the goal of the surgical cytoreduction was to remove all visible tumor by means of one or more of the following procedures: (1) greater omentectomy and left upper quadrant peritonectomy $\pm$ splenectomy; (2) right upper quadrant peritonectomy $\pm$ liver capsulectomy; (3) pelvic peritonectomy with total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), $\pm$ sigmoidectomy; (4) lesser omentectomy and dissection of the duodenal-hepatic ligament, $\pm$ cholecystectomy; (5) partial/total gastrectomy; (6) other procedures, including small bowel resections, right, transverse or total colectomy. Paraortic and pelvic lymphadenectomy was carried out in patients with clinically suspicious nodal involvement. All surgical specimens were submitted to pathological examination.

HIPEC was performed according to the closed-abdomen technique, with cisplatin (40 mg/l of perfusate) plus doxorubicin (15 mg/l of perfusate) for 90 min. Perfusate volume was 4–6 l, and average flow was 700 ml/min [30]. The temperature was monitored at 4 points (inflow/outflow catheters and upper/lower intra abdominal) and the drugs were instilled when intra-abdominal temperature achieved 42.5 °C. A 30% dose reduction was applied to patients >70 years old or those who underwent extensive surgical cytoreduction. No agents were used to prevent renal toxicity. The Performer LRT® [RAND, Medolla (MO), Italy] extracorporeal circulation device was used.

After hospital discharge, patients were referred to medical oncology staff to receive adjuvant systemic chemotherapy, consisting of 6 cycles of carboplatin (AUC 6) and paclitaxel (175 mg/m^2) administered every 21 days. Standard criteria for dose modification or delay were adopted. Physical examination, thoracic/abdominal CT-scan and Ca125 serum level assessment were performed every 3 months during the first 2 years and every 6 months thereafter. No patient was lost to follow-up.

Study parameters

Histological subtype and grade were assessed according to the WHO classification, and surgical stage according to the FIGO criteria [2].

The extension of previous surgical procedures was classified according to previous surgical score (PSS): PSS-0: 0 region dissected; PSS-1: 1 region dissected; PSS-2: 2–5 regions dissected; and PSS-3: >5 regions dissected [31]. The peritoneal cancer index (PCI) was used to score the extent of peritoneal involvement at surgical exploration. This index is based on lesion size and involvement of 13 abdominal regions with possible scores ranging from 0 (no disease) to 39 (widespread large volume disease involving all 13 regions)[31]. Completeness of cytoreduction (CC) was classified at the end of the surgical phase according to Sugarbaker criteria, as CC-0 (macroscopically complete); CC-1 (residual disease ≤ 2.5 mm in any region); CC-2 residual disease >2.5 mm [31]. Postoperative complications occurring within 30 days of the procedure were scored according to the NCI CTCAEv3 [32].

Statistics

The primary end-point of the present study was OS after CRS with HIPEC and followed by systemic carboplatin with paclitaxel. Secondary end-point was the assessment of treatment tolerability in terms of operative morbidity and TTC. Survival rates were calculated according to the Kaplan–Meier method. OS and PFS were dated from the day of CRS with HIPEC to the time of death due to any cause or postoperative disease progression, respectively. Patients with uneventful postoperative course were censored at the time of last follow-up visit or at the cut-off date, whichever occurred first. Operative mortality was included in survival rate calculation. TTC was calculated from the date of CRS and HIPEC to the day of first adjuvant systemic chemotherapy cycle.

Sample size was calculated considering the baseline median PFS of 17 months for advanced EOC treated by conventional surgery and systemic chemotherapy with carboplatin and taxol [33]. The aim was to have 80% power to detect a ratio of hazard rate of 2 using a one-sided and 5% significance level test after a 2-year continuation period. New eligible patients were estimated at the rate of one per month. The required accrual target was 24 patients with accrual time of

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24 months. Unfortunately due to difficulties in patients' recruitment the study period had to be extended. All statistical analyses were conducted by SPSS software version 18.0.0 for Windows (SPSS Inc., Chicago, IL). p-value <0.05 was considered significant.

Results

Twenty-six patients were prospectively enrolled during the accrual period. All the enrolled patients managed to undergo complete surgery. Patients' characteristics are shown in Table 1. The median interval between prior procedures and combined treatment was 2 months (range: 0.5–8). In all these patients, gross peritoneal disease was left after the aforementioned procedures.

Operative outcomes

Cytoreduction was rated as CC-0 in 15 patients and CC-1 in 11. Median PCI was 15.5 (range: 5–26). The details of CRS and HIPEC procedures are shown in Table 2. Median operative time was 620 min (range: 280–915); median postoperative hospital stay was 21 days (range: 13–67).

Four patients experienced 9 grade 3–5 complications. One patient developed grade 3 hematological toxicity, pleural effusion, requiring operative drainage, a subsequent abdominal abscess requiring reoperation, and ultimately died on the 39th postoperative day for sepsis. Operative complications are detailed in Table 3.

Except for one postoperative death, all the patients started adjuvant systemic chemotherapy. Median TTC was 46 days (range: 29–75). A median of 6 (range: 1–8) cycles per patient was given over a median of 20 weeks (range: 3–24). Disease progression and systemic toxicity caused treatment discontinuation in 2 patients, after 1 and 3 cycles, respectively. Four cycles were made with dose reduction. TTC did not impact on OS or PFS (data not shown).

Survival and failure

Median follow-up was 25 months (range: 1–70). At the time of the present analysis, peritoneal progression occurred in 8 patients, and liver progression in one; 16 patients are currently alive with no evidence of disease, 3 are alive with disease and 6 died (one postoperative death). Median PFS was 30 months and median OS was not reached; 5-year OS and PFS were 60.7% and 15.2% (Fig. 1).

Table 1
Patient characteristics.

Variables	Categories	*N*
Age	Median (range)	64 (26–78)
ECOG score	0	17
	1	6
	2	3
Previous surgical score	0: 0 region dissected	0
	1: 1 region dissected	18
	2: 2–5 regions dissected	8
	3: >5 regions dissected	0
Histological subtype	Serous adenocarcinoma	26
Grade	1	–
	2	4
	3	22
Stage	IIIb	1 24
	IIIc	24
	IV	1 (proximal vagina)
PCI	Median (range)	15.5 (5–26)
CA125	>35	24
	≤35	2

ECOG: Eastern Cooperative Oncology Group performance score; PCI: peritoneal cancer index.

Table 2
Cytoreductive surgical and HIPEC procedure.

Peritonectomies	*N*
Greater omentectomy	24
Right upper quadrant peritonectomy	16
Left upper quadrant peritonectomy	16
Pelvic peritonectomy	26
Lesser omentectomy	18
Visceral resections	
Splenectomy	10
Liver capsulectomy	3
Cholecystectomy	14
Partial gastrectomy	1
Sigmoidectomy	15
Right colectomy	9
Total colectomy	3
Small bowel resection	3
Total hysterectomy[a]	18
Bilateral salpingo-oophorectomy[b]	19
Appendectomy	3
Para aortic and pelvic lymphadenectomy	4
Proximal vagina resection	1
Other	2
Ileostomy[c]	11
HIPEC	
Cisplatin total dose, median (range)	150 mg (80–250)
Doxorubicin total dose, median (range)	70 mg (40–80)

HIPEC: hyperthermic intraperitoneal chemotherapy; SD: standard deviation.
[a] Eight patients underwent TAH previously (two of them for non-neoplastic cause).
[b] Seven patients underwent BSO previously.
[c] No colostomy was done.

Discussion

To the best of our knowledge, this is the first study assessing the oncological outcome after CRS and HIPEC for advanced EOC in newly diagnosed and treatment-naïve disease setting. The only previous experience of upfront CRS and HIPEC in EOC has been reported in a phase-I study [34]. Five-year OS and PFS were 60.7% and 15.2%, respectively; operative mortality was 3.8% and severe morbidity 15.2%. Our data demonstrate that such a comprehensive approach is a feasible and safe upfront therapy option, with potential benefits that are at least comparable with the current standard of care.

Although there is no universally accepted definition of optimal cytoreduction for advanced EOC, the inverse correlation between survival and postsurgical residual tumor size has been shown by multiple retrospective series [35]. Recently, Chi has reported the outcomes of a more aggressive surgical policy adopted since 2001 at

Table 3
Post operative adverse events.

	N. of patients	%	CTCAE grade	Treatment
Operative death	1	4		
Reoperation	1	4		
Grade 3–5 morbidity	4	15		
Types of complications ($n=9$)				
Hematological toxicity	1	4	3	Medical therapy
Pneumothorax	1	4	3	Operative drainage
Pleural effusion	1	4	3	CT-scan guided drainage
Abdominal abscess	1	4	4	Reoperation
Sepsis	1	4	5	Medical therapy, ICU
Pneumonia	1	4	3	Medical therapy
Central line infection	1	4	3	Medical therapy
Colorectal anastomosis bleeding	1	4	3	Interventional endoscopy
Bladder fistula	1	4	3	Interventional radiology

ICU: intensive care unit.

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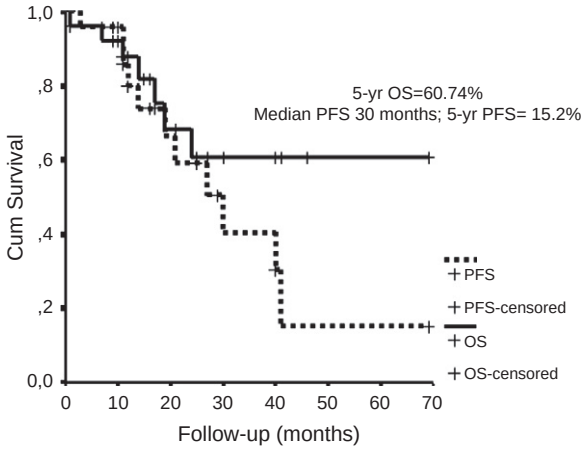

Fig. 1. Overall survival of patients affected by advanced epithelial ovarian cancer treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Table 4
Literature data on upfront treatment of advanced epithelial ovarian cancer.

	Stage	*N*	Treatment	Median OS (months)	5 year OS	Median PFS (months)	5 year PFS
Armstrong [18]	III	214	CRS + IP CT	65.6		23.8	
		215	CRS + IV CT	49.7		18.3	
Vergote [6]	IIIc and IV	334	NACT	30.0		12.0	
		336	Conventional upfront CRS	29.0		12.0	
Eisenkop [36]	IIIc	408	Maximal surgical effort	58.2	49.0%		
Chi [15]	IIIc and IV	210	Maximal surgical effort	54.0	47.0%		31.0%
Present series	IIIc and IV	26	CRS + HIPEC	Not reached	60.7%	30.0	15.2%

his center. Such a paradigm shift has resulted in higher rates of optimal cytoreduction (80% vs. 46%; p-value = 0.01), improved 5-year PFS (31% vs. 14%; p-value = 0.01) and 5-year OS (47% vs. 35%; p-value = 0.03), as compared to a control group receiving standard operations [15]. The need for a macroscopically complete cytoreduction has been addressed by Eisenkop[6], who showed better survival over minimal residual disease (<1 cm) [36]. Furthermore, in an exhaustive meta-analysis of 81 series accounting for 6995 patients treated during the platinum era, Bristow demonstrated a 5.5% increase in median survival, with each 10% increase in the percentage of patients undergoing maximal cytoreduction [14].

The benefit of loco-regional chemotherapies has been shown by three phase-III trials comparing intravenous with intravenous plus intraperitoneal chemotherapy following optimal surgery for advanced EOC [16–18]. Treatment-related morbidity, particularly complications associated with prolonged drug administration and catheters implantation through the abdominal wall, seems to be the major limitation of loco-regional chemotherapy. In the landmark study by Armstrong, only 40% of patients completed the six courses of intraperitoneal chemotherapy, but the survival benefit was still demonstrable [18]. Successively, a Cochrane meta-analysis showed a hazard ratio of 0.79 for both disease-free and OS, in favor of loco-regional administration [37]. Nevertheless, complete, or even "optimal" cytoreduction [38] and intraperitoneal chemotherapy [39] are still not routinely offered in the current clinical practice.

The combined approach assessed in the present study take advantages of both aggressive CRS and loco-regional chemotherapy, but it also represents a further development which may overcome their inherent limitations. The advent of the peritonectomy procedure has brought a systematic optimization of CRS, and an accurate codification of the surgical steps to obtain the macroscopically complete resection of huge peritoneal tumor [28,29]. Different from the intraperitoneal chemotherapy used in the Armstrong and other GOG trials, HIPEC is performed intraoperatively to allow optimal distribution throughout the abdominal cavity before the development of postoperative adhesions. This prevents tumor cell entrapment in scar tissue, which can give rise to disease recurrence. Most importantly, HIPEC avoids implanting any peritoneal access device [28].

The present report suggests promising OS and PFS, compared to either randomized and non-randomized contemporary or historical control populations [6,15,18,36]. In Table 4 we outlined the most recent studies on front-line therapy of advanced EOC. Our data seem to be better than those of Vergote who tested NACT compared to conventional first-line cytoreduction. On the other hand our data are in line with those of Armstrong who used normothermic IP chemotherapy and with those reported by Eisenkop and Chi who employed the maximum surgical effort in front-line cytoreduction.

One could argue that the good OS and PFS results were obtained thanks to selection bias and that complete cytoreduction in most cases was achievable due to relatively small tumor burdens and presumed diminished tumor biological aggressiveness rather than to maximal surgical effort [40]. According to Eisenkop the need to remove a large number of peritoneal implants could be linked with biological aggressiveness and poorer outcome, but not significantly enough to justify abbreviation of the surgical effort [41]. On the other hand, an exploratory analysis in the context of a large randomized trial (SCOTROC) has shown a significant benefit in PFS correlated with optimal surgery in stage IIIC to IV disease, that is limited to patients with less advanced disease [42].

The question of relative influence of tumor biology and actual impact of CRS on outcome has been elucidated by a study evaluating tumor-infiltrating lymphocytes and/or mitotic activity in 134 patients with advanced serous or poorly differentiated EOC undergoing primary CRS [43]. Patients with aggressive tumors—low frequency of intraepithelial CD8(+) T-cells or high Ki67 expression—were more likely to benefit from aggressive CRS. On the other hand, survival was similar for patients with brisk CD8(+) T-cells or low Ki67 who had optimal or suboptimal cytoreduction. The study represents the first biological evidence that optimal cytoreduction is not a direct consequence of a favorable biology, and that aggressive surgical approach is justified in more aggressive disease.

As with any other oncologic therapy, the ideal time point to obtain the best result is primary treatment, when no previous extensive surgical and systemic therapies have likely resulted in diffuse peritoneal adhesions, further disease dissemination, emergence of possible chemoresistance and compromised patient conditions [13]. Therefore it seems reasonable that this combined approach is used early in the natural history of EOC, ideally at first diagnosis of advanced disease.

Little has been reported on front-line use of CRS and HIPEC [6,19,20,23,24,34]. As a first necessary step before planning a randomized trial, the current study provided the evidence of the feasibility, safety and survival of the combined approach. The management of EOC should incorporate both loco-regional and systemic therapy, since peritoneal and both lymphatic and hematogenous spread may occur with disease progression [25]. Intraoperative HIPEC allows microscopic residual disease to be treated many days prior to conventional chemotherapy, and, as our data strongly suggest, do not hinder the subsequent administration of systemic carboplatin and paclitaxel.

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Another criticism against the employment of an aggressive surgical approach in upfront setting is the presumed increased morbidity that could be avoided with NACT option. Rates of optimal cytoreduction could increase and surgical effort after systemic therapy is expected to be less extensive. In a large randomized study similar results in terms of PFS and OS between the NACT and non NACT arms have been reported [6]; no conclusions have been drawn concerning the morbidity due to non-comparability of the groups. These results were in line with those of a recent meta-analysis [44]. To our knowledge no literature data on the combined treatment after NACT are available.

Mortality and morbidity in the present study are acceptable and accords with literature, reporting operative complication and death rates of 12–52% and 0.9–5.8%, respectively [45]. Aggressive cytoreduction without HIPEC is associated with similar major morbidity rates (12–60%) and in a retrospective review of 20 single-center series, mean operative mortality was 2.8% (range: 0–6.2%) [46]. Unfortunately, one operative death occurred in 26 procedures (3.8%).

All the patients underwent systemic chemotherapy at a median of 46 days from combined treatment, which represents a relative delay as compared to TTC of 21–26 days reported in the literature [26,47–49]. There is no consensus on the prognostic significance of TTC. Some authors have reported a worse PFS for those with earlier treatment [49], while Warwick have reported a negative impact of longer TTC on survival [48]. Others have reported absence of correlation between TTC and outcome [26,47]. Patients in our study with TTC>46 days did not present a worse survival as compared to those with shorter TTC, despite the delay of about 20 days in the median TTC with respect other experiences. We raised the hypothesis that a microscopic cytoreduction exerted by HIPEC neutralized eventual disease progression after surgery allowing that longer TTC did not assume a negative prognostic role.

In conclusion, this phase-II trial demonstrated favorable results in terms of OS after upfront CRS and HIPEC for advanced EOC. Additionally, this challenging procedure was associated with acceptable operative complications and timely administration of effective adjuvant systemic chemotherapy, even if performed in general hospitals with appropriate training. This information may help planning future phase-III trials.

Conflict of interest

The authors do not have any conflict of interest to disclose.

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