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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in epithelial ovarian cancer: State of the art

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describing oncologic outcomes in EOC patients treated with HIPEC in the primary setting.

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Key words: Epithelial ovarian cancer; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Intraperitoneal chemotherapy; Survival; Toxicity

Core tip: Hyperthermic intraperitoneal chemotherapy (HIPEC), when used in combination with successful surgical cytoreduction appears to result in promising oncologic outcomes. We will eagerly await the results of the various phase 3 clinic trials, and until that time advocate the use of cytoreductive surgery + HIPEC in experienced centers under the auspices of appropriate institutional research programs.

Abstract

Advanced stage epithelial ovarian cancer (EOC) is difficult to treat with low overall cure rates. A new strategy combining maximal cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has been proposed to treat advanced stage EOC in the primary setting. Numerous small, heterogeneous studies have been conducted exploring outcomes in patients with predominantly advanced, recurrent or refractory disease treated with CRS + HIPEC. Although morbidity rates approaching 35% have been reported, oncologic outcomes are promising. Incorporation of HIPEC for the treatment of primary EOC has continued to gain interest. Several prospective phase 2 clinical trials were recently completed evaluating the impact of CRS + HIPEC in the primary setting. This article will briefly discuss the benefits of optimal surgical cytoreduction and the theoretical basis of intraperitoneal chemotherapy in patients with advanced stage EOC, and will then review existing literature

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INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for 25% of all malignancies affecting the female genital tract, and is the most lethal gynecologic malignancy^[1]. In 2012 there will be an estimated 22280 new ovarian cancer cases in the United States, with 15500 deaths^[1]. Advanced stage EOC is traditionally managed with surgery, followed by platinum and taxane based combination chemotherapy^[2,3].

Several factors have been identified as prognostic

for clinical outcome in patients with EOC, with extent of residual disease being investigated in numerous studies^[4]. Specifically, a differential survival impact between patients with no gross residual disease *vs* optimal but visible residual disease (0.1-1.0 cm in maximal diameter) has been illustrated in patients with optimally resected stage 3 EOC^[4]. These findings have been validated by other authors^[5,6]. Currently, the Gynecologic Oncology Group (GOG) defines optimal residual disease as ≤ 1 cm. The reason cytoreductive surgery (CRS) is thought to be effective when combined with chemotherapy is that it removes bulky disease containing poorly oxygenated, non-proliferating cells which are either resistant or potentially resistant to chemotherapy, leaving small volume tumors, with a higher proportion of cells in the proliferative phase, that are more susceptible to chemotherapy^[7].

In addition to aggressive CRS, our understanding of the distribution pattern of ovarian cancer catalyzed numerous clinical studies exploring the feasibility of intraperitoneal administration of chemotherapy. Ovarian cancer typically spreads in a diffuse intra-abdominal fashion, often limited to the peritoneal cavity, less frequently metastasizing *via* hematogenous or lymphatic routes. Despite advanced surgical techniques, microscopic tumor implants commonly remain along the peritoneal surface. Animal models suggested the ability of intraperitoneal administration of cytotoxic agents to lead to cancer cell death in lesions measuring 2-3 mm in largest diameter^[8]. Therefore, successful CRS is a main pre-requisite for intraperitoneal administration of chemotherapy^[9]. Furthermore, due to the presence of a peritoneal-plasma barrier, chemotherapeutic agents remain concentrated (20-1000 fold) in the peritoneal cavity for a prolonged period of time resulting in enhanced cancer cell death, with theoretically less systemic toxicity^[7,10,11].

Three pivotal clinical trials were completed evaluating the impact of intraperitoneal (IP) chemotherapy on survival in patients with advanced stage ovarian cancer^[12-14]. Initially, 2 randomized phase 3 intergroup trials comparing intravenous (IV) to IV + IP chemotherapy showed positive results. The GOG subsequently developed and opened protocol 172, which compared IV paclitaxel (135 mg/m²) over 24 h with IV cisplatin (75 mg/m²) on day 2, *vs* IV paclitaxel (135 mg/m²) over 24 h, followed by IP cisplatin (100 mg/m²) on day 2 and IP paclitaxel (60 mg/m²) on day 8. A total of 6 courses were administered every 3 wk^[14]. All patients had optimally resected disease with residual tumor limited to less than or equal to 1 cm in size. The median survival for the IV only and IV + IP arms were 49.5 and 66.9 mo respectively. The RR of death was 0.71 in the IP group ($P = 0.0076$). The authors noted that tolerability for IP chemo was a concern as grade 3 and 4 hematologic, metabolic, and gastrointestinal toxicities were significantly more common in the IP arm. Remarkably, only 86 patients (42%) of 205 allocated to the IP arm completed 6 cycles of chemotherapy, and 98 (48%) received 3 cycles or fewer of the assigned treatment.

The results of GOG 172, in combination with previous positive studies exploring intraperitoneal chemotherapy, resulted in a National Cancer Institute (NCI) clinical announcement recommending that women with optimally cytoreduced stage 3 ovarian cancer be considered for IV + IP therapy^[15]. Unfortunately, adoption of the IP regimen described in protocol 172 has been limited, due to the high rate of grade 3/4 toxicities, inconvenience of in-patient administration, and poor patient tolerance.

Attempts at modification of the original regimen have been made in an effort to improve compliance and decrease toxicity. Barlin *et al*^[16] investigated the oncologic outcomes associated with an outpatient IP regimen in 102 patients with optimally cytoreduced EOC. The modified regimen consisted of IV paclitaxel (135 mg/m²) over 3 h on day 1, IP cisplatin (75 mg/m²) on day 2, and IP paclitaxel (60 mg/m²) on day 8, given every 21 d for 6 cycles. The median PFS and OS were 29 and 67 mo, respectively. Importantly, 80% of subjects completed 4 or more cycles of IV + IP therapy. The most frequently reported grade 3/4 toxicities included neutropenia (12%), gastrointestinal (8%) and neurologic (6%)^[16]. GOG protocol 252, which completed accrual in November 2011, will help elucidate the role of intraperitoneal chemotherapy in patients with optimally resected EOC, as well as the potential role of both dose dense paclitaxel and the anti-angiogenic agent bevacizumab.

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

In an effort to obviate the toxicities encountered with repetitive cycles of intraperitoneal chemotherapy, investigators have explored the use of a single course of intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) followed by conventional intravenous chemotherapy. The concept of HIPEC is based on several important principles: (1) the direct and preferential cytotoxic effect of hyperthermia on tumor cells; (2) synergistic effects of hyperthermia when used with conventional cytotoxic agents without an associated increase in toxicity; and (3) increased drug penetration, from 3 to 5 mm, secondary to hyperthermia^[17-24].

In addition, the presence of extensive adhesions in the post-operative period are hypothesized to result in both impaired drug distribution and significant toxicity/pain when traditional IP chemotherapy is given in the adjuvant setting. Utilization of intra-operative HIPEC, at the time of initial CRS, guarantees uniform distribution and systemic peritoneal coverage, potentially enhancing the anti-tumor efficacy of the drugs used.

Based on the theoretical principles described above, HIPEC was first examined in patients with peritoneal carcinomatosis due to gastrointestinal malignancies, *pseudomyxoma peritonei* and peritoneal mesothelioma^[25-28]. In the surgical setting, these trials illustrated the safety and feasibility of hyperthermic intraperitoneal drug administration.

Table 1 Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy in the treatment of advanced stage primary epithelial ovarian cancer: retrospective and observational studies: Study characteristics

Ref.	n	Disease stage	Setting of treatment	HIPEC drug and dose	Temp. (°C)	Duration of treatment (min)	Oncologic outcome	Common grade 2-3 toxicities	Mortality rate
Tentes <i>et al</i> ^[8]	43	"Locally advanced" ovarian cancer	23 primary 20 recurrent	Doxorubicin 15 mg/m ² + Cisplatin 50 mg/m ² or Gemcitabine 1000 mg/m ²	42.5-43	60 or 90	5-yr OS: 54% In primary population 5-yr OS 82.5%	Hematologic; GI; infectious	2 deaths (sepsis)
Steller <i>et al</i> ^[31]	6	2-3 EOC	2 primary 4 recurrent	Carboplatin 800-1200 mg/m ²	42	90	All alive at 15 mo follow up; 5 without evidence of disease	Hematologic	No deaths
Piso <i>et al</i> ^[33]	19	3-4 EOC	8 primary 11 recurrent	Cisplatin 75 mg/m ² + Mitoxantrone 15 mg/m ²	41.5	90	Median PFS 18 mo; mean OS 33 mo; 5 yr survival 15%	Hematologic; GI (anastomotic leak, fistula); bleeding; abscess	1 death (sepsis)
Rufián <i>et al</i> ^[35]	33	3 EOC	19 primary 14 recurrent	Paclitaxel 60 mg/m ²	41-43	60	In primary population median relapse free survival was 25 mo; median OS 38 mo	Hematologic; infectious; GI (bleeding and perforation)	No deaths
Lentz <i>et al</i> ^[37]	25	3 EOC	11 primary 14 recurrent	Carboplatin 400-1200 mg/m ²	Inflow < 43.5	90	Not reported	One PE; one superficial wound dehiscence	No deaths
Pavlov <i>et al</i> ^[39]	56	3-4 EOC	31 primary 25 recurrent	Doxorubicin 0.1 mg/kg + Cisplatin 15 mg/m ²	40	180	Median OS 38.1 mo; 5-yr OS 67%	Hematologic; GI (anastomotic leak, obstruction)	1 death (CVA)

HIPEC: Hyperthermic intraperitoneal chemotherapy; Temp.: Temperature; OS: Overall survival; GI: Gastrointestinal; EOC: Epithelial ovarian cancer; PFS: Progression free survival; PE: Pulmonary embolism; CVA: Cerebral-vascular accident.

HIPEC AND OVARIAN CANCER

Observational and retrospective studies

In 1990, Cohen and Robins proposed HIPEC for the treatment of recurrent ovarian cancer^[29,30]. Steller *et al*^[31] studied the feasibility, toxicity and pharmacokinetics of intraperitoneal hyperthermic carboplatin administration in 6 patients at the time of primary surgical cytoreduction. Shortly thereafter, Hager *et al*^[32] conducted a prospective clinical trial on 36 patients with recurrent ovarian cancer treated with CRS and HIPEC. The median OS from the first HIPEC chemotherapy treatment was 19 ± 4 mo. The 5-year OS of all patients from the start of the first HIPEC treatment was 16% ± 7%. The authors described the adverse effects as mild when compared to systemic chemotherapy.

This was followed by a study conducted by Piso *et al*^[33] of 19 patients with peritoneal carcinomatosis due to primary or recurrent EOC. Surgery was followed by intraoperative HIPEC using single agent cisplatin ($n = 16$) or mitoxantrone ($n = 3$). The median progression free interval was 18 mo (range 6-36 mo), with mean overall survival time of 33 mo and a 5-year survival rate of 15%. The most common complications encountered were anastomotic leak (2 of 19) and intra-abdominal abscess formation (2 of 19)^[33]. Additional studies evaluating the clinical effect of HIPEC in patients with advanced stage ovarian cancer were completed in an effort to determine the most appropriate/effective chemotherapeutic agent and the ideal hyperthermic temperature (Table 1)^[8,34-39].

Ryu *et al*^[34] retrospectively reviewed 117 patients with ovarian cancer, 57 who underwent CRS (conventional treatment) with HIPEC and 60 who underwent conven-

tional treatment only. The investigators studied a HIPEC mixture consisting of carboplatin (350 mg/m²) and interferon- α (5000000 IU/m²). Intraperitoneal temperature was maintained at 43-44 °C during surgery. The overall 5-year survival rate was significantly greater in the HIPEC group *vs* control (63.4% *vs* 52.8%, respectively, $P = 0.0078$). This survival advantage was more pronounced amongst the subset of patients with stage 3 disease (53.8% in the HIPEC group *vs* 33.3% in the control group, $P = 0.0015$). In multivariate analysis, HIPEC was identified as an independent prognostic factor.

HIPEC was also studied in the recurrent setting. Zanon *et al*^[40] examined the use of combined CRS and HIPEC in 30 women with recurrent EOC. Enrolled subjects underwent extensive CRS followed by intraoperative HIPEC with cisplatin (100-150 mg/m²). In patient's cytoreduced to ≤ 2.5 mm of residual disease, progression free survival was 17.1 mo, with an overall survival of 37.8 mo. Major post-operative morbidity occurred in 16.7% of subjects, with gastrointestinal toxicities (anastomotic leak and perforations) being the most commonly reported. One treatment related mortality, a fatal pulmonary embolism, occurred 30 d following discharge. Cotte *et al*^[41] prospectively studied combination CRS + HIPEC in 81 patients with recurrent or chemotherapy resistant peritoneal carcinomatosis from ovarian cancer. Mortality and morbidity rates were 2.5% and 13.6%, respectively. With a median follow-up of 47.1 mo, the overall and disease-free median survivals were 28.4 and 19.2 mo, respectively.

HIPEC in combination with secondary cytoreduction was further investigated as consolidation therapy in patients with advanced stage EOC following surgery and systemic intravenous chemotherapy^[29,42-44]. Within this

Table 2 Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy in the treatment of advanced stage primary epithelial ovarian cancer: prospective phase 2 trials

Ref.	n	Disease stage	Setting of treatment	HIPEC drug used and dose	Temp. (°C)	Duration of treatment (min)	OS (mo)	PFS (mo)	Common grade 2-3 toxicities	Mortality rate
Di Giorgio <i>et al</i> ^[47]	47	3C-4 EOC	22 primary 25 recurrent	Cisplatin 75 mg/m ²	42-43	60	30.4 (mean)	27.4 (mean)	Pleural effusions (8.5%) Infectious (8.5%) GI (10.6%) Bleeding (6.4%)	4% (PE)
Lim <i>et al</i> ^[48]	30	3-4 EOC	30 primary (14 of which underwent neoadjuvant treatment)	Cisplatin 75 mg/m ²	41.5	90	NR	NR	Hematologic (86.7%) GI (30%) Infectious (16.7%) Pulmonary (23.3%) CV (13.3%)	No deaths
Ansaroni <i>et al</i> ^[49]	26	3-4 EOC	26 primary	Cisplatin 40 mg/L perfusate + doxorubicin 15 mg/L perfusate	42.5	90	Not reached 5-yr OS 60.7%	30 (median) 5-yr PFS 15.2%	Hematologic (4%) GI (4%) Pulmonary (14.3%) Infectious (14.3%)	4% (sepsis)

Ninety-three percent with complete response to primary treatment. Seven patients with progressive disease. HIPEC: Hyperthermic intraperitoneal chemotherapy; Temp.: Temperature; OS: Overall survival; PFS: Progression free survival; EOC: Epithelial ovarian cancer; GI: Gastrointestinal; PE: Pulmonary embolism; NR: Not reported; CV: Cardiovascular.

cohort of patients, HIPEC (cisplatin 100 mg/m²), when given at the time of “second-look” laparotomy, resulted in an improvement in the 5-year survival rate, although the difference did not reach statistical significance (57.9% in HIPEC group *vs* 44.8% in the control group). This was attributed to the small sample size studied (29 subjects). Notably, no HIPEC associated grade 3 or 4 toxicities were reported. An analogous study conducted by Yoshida *et al*^[42] demonstrated marked median progression-free and overall survival rates in subjects treated with HIPC who had a negative second look laparotomy (82.8 and 130.3 mo, respectively).

Investigators from The NCI of Milan studied outcomes associated with CRS and HIPEC in patients with advanced, recurrent ovarian cancer previously treated with systemic cisplatin-based, taxol-based or taxol/platinum containing regimens^[45]. Within the cohort of 40 patients, 5-year OS was 15%, with mean OS and PFS of 41.4 and 23.9 mo, respectively. The morbidity, toxicity and mortality rates were 5%, 15% and 0%, respectively. Dr. Helm *et al*^[46] retrospectively evaluated the use of secondary CRS + HIPEC in patients with disease resected to ≤ 5 mm. The regimens used in the study consisted of cisplatin (100 mg/m² in 15 patients) or mitomycin C (30-40 mg total dose in 3 patients) heated to 41-43 °C (105.8-109.4 degrees F) for 90 min. All patients developed grade 1 or 2 metabolic or hematologic toxicities. Grade 3 or 4 metabolic toxicity occurred in 72% and hematologic toxicity in 28%. There was one perioperative death due to pulmonary embolus. The median progression-free interval was 10 mo and median overall survival was 31 mo.

Prospective phase 2 clinical trials

The trials described above were limited by their retrospective nature, small sample size, heterogenous patient population and variation in both dose and drug used.

These limitations prompted the creation and completion of larger prospective phase 2 clinical trials specifically exploring CRS + HIPEC in the up-front treatment of patients with advanced EOC (Table 2).

The first phase 2 clinical trial exploring the use of HIPEC in patients with primary advanced ovarian cancer was completed in 2007^[47]. Forty-seven patients were enrolled in this open, prospective, single-center nonrandomized study; 22 underwent primary and 25 secondary CRS plus immediate HIPEC (cisplatin 75 mg/m²) followed by systemic chemotherapy. Eighty-seven percent of the patients achieved optimal cytoreduction, whereas macroscopic residual disease (defined as lesions ≥ 2.5 mm) was left behind in 12.7% of subjects. Major complications (gastrointestinal fistula, intra-abdominal bleeding and thrombosis) developed in 21.3% of the patients and the in-hospital mortality rate was 4.2% (2 patients with pulmonary embolism). The mean overall survival was 30.4 mo, median survival was 24 mo, and mean disease-free survival was 27.4 mo. Five-year survival was 16.7%.

This was followed by a study investigating the morbidity and feasibility of CRS + HIPEC in patients with advanced stage primary EOC. Lim *et al*^[48] treated 30 patients with residual tumor measuring < 1 cm at the time of primary surgery, with intraoperative HIPEC (cisplatin 75 mg/m²) at a temperature of 41.5 °C for 90 min. All the patients subsequently received adjuvant chemotherapy with combination IV platinum and taxane. Within the cohort, 28 patients (93%) experienced complete remission, and only two patients (7%) had progressive disease. The most commonly reported toxicities included nausea/vomiting, anemia, diarrhea, pleural effusions and wound infections. No deaths or morbidities requiring reoperation or intensive care unit admission were reported. The overall survival data was not yet mature given the interim nature of the evaluation.

Ansaroni *et al.*^[49] in their open, prospective phase 2 study, included thirty-nine patients. Thirty patients (77%) had recurrent EOC and 9 (23%) had primary EOC. For HIPEC, cisplatin and paclitaxel were used for 11 patients (28%), cisplatin and doxorubicin for 26 patients (66%), paclitaxel and doxorubicin for 1 patient (3%), and doxorubicin alone for 1 patient (3%). All HIPEC were performed with open technique. The median intra-abdominal outflow temperature was 41.5 °C. The mean peritoneal cancer index (PCI) was 11.1; according to the intraoperative tumor extent, the tumor volume was classified as low (PCI < 15) or high (PCI ≥ 15) in 27 patients (69%) and 12 patients (31%), respectively. Microscopically complete cytoreduction was achieved for 35 patients (90%), macroscopic cytoreduction was achieved for 3 patients (7%), and a gross tumor debulking was performed for 1 patient (3%). Mean hospital stay was 23.8 d. Grade I–III post-operative complications occurred in 7 patients (18%), and reoperations in 3 patients (8%). There was one postoperative death. Recurrence was seen in 23 patients (59%) with a mean recurrence time of 14.4 mo (60).

More recently, a multi-institutional phase 2 study was completed evaluating the impact of CRS + HIPEC on PFS and OS in 26 women with stage 3–4 EOC^[50]. All enrolled subjects underwent CRS, followed by HIPEC using the closed-abdomen technique with cisplatin (40 mg/L perfusate) and doxorubicin (15 mg/L of perfusate). Patients were then treated with 6 cycles of adjuvant IV carboplatin (AUC 6) and paclitaxel (175 mg/m²) administered every 3 wk. Macroscopically complete cytoreduction was achieved in 15 patients (57%), with minimal residual disease (≤ 2.5 mm) remaining in the other 11 (43%). After a median follow-up of 25 mo, 5-year overall survival was 60.7% and 5-year progression-free survival 15.2% (median 30 mo). Excluding operative death, all the patients underwent a median of 6 cycles of systemic chemotherapy at a median of 46 d from combined treatment (range: 29–75 d)^[50]. Four patients experienced ≥ grade 3 morbidity, with one post-operative death due to sepsis.

In conclusion, the incorporation of HIPEC in the treatment of primary advanced stage ovarian cancer has shown promising results in both observational studies as well as phase 2 clinical trials. The only randomized phase 3 clinical trial exploring the impact of HIPEC on survival was conducted in patients with carcinomatosis associated with colorectal cancer, showing a significant improvement in survival amongst patients allocated to the HIPEC arm^[28]. Unfortunately, patients randomized to the non-HIPEC arm of the trial did not undergo aggressive CRS, potentially impacting survival and limiting the clinical implications of the study^[28].

To date, no randomized phase 3 clinical trials have been completed evaluating the impact of HIPEC on survival in patients with advanced stage ovarian, fallopian tube or primary peritoneal carcinoma. Furthermore, the use of non-randomized contemporary or historical control populations restricts the generalizability of results reported in the trials discussed above^[51]. In order to address

this important clinical question, 4 randomized phase 3 clinical trials are currently in various stages of design and implementation^[49].

As with any new therapeutic paradigm, the benefits of HIPEC in the treatment of patients with ovarian cancer must be weighed against the side effects. Overall, HIPEC appears to be well tolerated in appropriately selected patient populations. Nonetheless, toxicity and mortality rates as high as 35% and 5%, respectively, have been reported^[52]. Given the relative novelty of this approach, improvements in patient outcome and mitigation of toxicities experienced have been described by more experienced centers^[53–58]. Furthermore, quality of life studies have indicated improved emotional well being and rapid return to pre-operative levels of functioning following HIPEC treatment^[59].

In summary, HIPEC, when used in combination with successful surgical cytoreduction appears to result in promising oncologic outcomes. We will eagerly await the results of the various phase 3 clinic trials, and until that time advocate the use of CRS + HIPEC in experienced centers under the auspices of appropriate institutional research programs.

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