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Current Status and Future Prospects of Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIPEC) Clinical Trials in Ovarian Cancer

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Abstract

The natural history of advanced-stage epithelial ovarian cancer is one of clinical remission after surgery and platinum/taxane-based intravenous and/or intraperitoneal chemotherapy followed by early or late recurrence in the majority of patients. Prevention of progression and recurrence remains a major hurdle in the management of ovarian cancer. Recently, many investigators have evaluated the use of normothermic and hyperthermic intraoperative intraperitoneal drug delivery as a management strategy. This is a narrative review of the current status of clinical trials of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in ovarian cancer and the future directions for this treatment strategy. The existing studies on HIPEC in patients with epithelial ovarian cancer are mostly retrospective in nature, are heterogeneous with regards to combined inclusion of primary and recurrent disease, and lack unbiased data. Until data are available from evidence-based trials, it is reasonable to conclude that surgical cytoreduction and HIPEC is a rational and interesting, though still investigative, approach in the management of epithelial ovarian cancer, whose use should be employed within prospective clinical trials.

Keywords

ovarian cancer; surgery; hyperthermic intraoperative intraperitoneal chemotherapy; HIPEC; clinical trials

I. Introduction

Ovarian cancer is the second most common gynecologic malignancy and the fifth leading cause of death among American women, with an estimated 14,240 deaths in 2016 [1].

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Declaration of Interest Statement

The authors report no conflicts of interest.

Advances in surgical cytoreduction and chemotherapy have steadily improved the median overall survival (OS) in these patients over the last four decades [2]. Most patients with epithelial ovarian cancer present with overt peritoneal disease. The natural history of advanced-stage ovarian cancer is one of clinical remission after surgery and platinum/taxane-based chemotherapy followed by recurrence in the majority of women, with long-term cure rates languishing between 20–25% [3].

In most cases of advanced epithelial ovarian cancer, the bulk of the tumor is located within the peritoneum. Due to this predilection for the peritoneal cavity, numerous theoretical studies have evaluated the use of intraperitoneal (IP) drug delivery as a management strategy for ovarian cancer. The studies reported a pharmacologic advantage for IP versus intravenous (IV) delivery of chemotherapy, with improved tumor cell access, longer half-life in the peritoneal compartment, increased dose intensity, and slow peritoneal clearance, while still reaching sufficient levels of systemic exposure for longer periods of time [4–7]. Although IP treatment is associated with improved survival, it has not been widely adopted as standard of care due to concerns of excessive toxicity, difficult logistics, and cost [8]. Hyperthermic IP chemotherapy (HIPEC) is a proposed method of intraoperative IP chemotherapy delivery that may eliminate some of the issues associated with standard IP therapy, possibly making it a viable therapeutic option in this setting [9]. However, the role of HIPEC for patients with ovarian cancer remains controversial, as efficacy, safety concerns, costs, and patient selection criteria are the subject of ongoing debate without sufficient randomized data. [10]. The objective of this article is to provide a narrative review of the current status and future directions of HIPEC utilization in ovarian cancer.

II. Background of HIPEC

HIPEC differs distinctly from postoperative IP delivery in that it is a single treatment of intraoperative chemotherapy at the time of cytoreductive surgery. This approach has been explored in the treatment of patients with other peritoneal malignancies, including pseudomyxoma peritonei, mesothelioma, and appendiceal and colorectal malignancies [11–15]. It has the following proposed advantages: i) by giving the chemotherapy intraoperatively, drug exposure is optimal secondary to direct contact with the remaining microscopic cancer cells without the barriers of postoperative adhesions; ii) intraoperatively, the chemotherapy can be delivered under highly standardized procedures, and the surgeon can guarantee optimal distribution of the chemotherapy and control dwell times; and iii) hyperthermia has been shown to increase the cytotoxic effect of many chemotherapeutic agents by increasing DNA-crosslinking and increasing tumor penetration [16–18].

The precise cytotoxic mechanisms associated with supranormal temperatures are unclear. In initial studies, temperatures in the range of 42–45°C for 10–60 minutes were shown to cause lethal damage [19]. The toxic effects include alterations in the cell membrane and nucleus, protein denaturation, and changes in calcium permeability. Although hyperthermia may affect normal tissues, the heat effect disproportionately affects hypoxic tumor cells due to the relative poor perfusion and acidotic, malnourished setting [20]. Hyperthermia also appears to increase sensitivity to chemotherapeutic agents, particularly cisplatin, in both platinum-sensitive and platinum-resistant cell lines [20]. The increased cytotoxicity appears

to be related to enhanced intracellular drug accumulation and adduct processing. In vitro studies have shown that treatment of the tumor cells with both hyperthermia and platinum lead to an increase in the number of platinum-DNA adducts and an additive cytotoxic effect related to disease response [17, 18, 21].

Despite the numerous studies and reviews published on HIPEC and ovarian cancer in the last few years, there is currently limited evidence from randomized prospective trials to definitively determine any survival benefit associated with this approach for patients with advanced ovarian cancer. A PubMed search using the search terms “HIPEC and ovarian cancer” yields 247 results, reflecting the increasing investigation of this treatment modality. However, systematic review of these data demonstrate heterogeneity regarding inclusion criteria, drug regimen, procedure technique, and methods of reporting survival outcomes [22]. For example, many studies include both primary and recurrent disease, platinum-resistant and platinum-sensitive disease, and use multiple chemotherapeutic agents [22, 23]. Consequently, the role of HIPEC for patients with ovarian cancer remains contentious.

III. Technique

Studies have explored various methods and mechanisms for surgical approach and hyperthermic chemotherapy delivery. There is a wide variation in the methodology of HIPEC treatment. A 2015 survey of 34 different French teams found a lack of uniformity in HIPEC technique [24]. Even though many of the participants were from expert institutions and had been involved in training members from the other teams, there were differences with regard to open versus closed techniques, equipment used, protective mechanisms, and training [24].

Internationally, there is minimal uniformity in drug regimen, temperature, and treatment duration [22]. Most studies use at least one platinum-based agent, most commonly cisplatin, oxaliplatin, or carboplatin [9, 22]. Some evidence suggests that carboplatin may be a better option in ovarian cancer [9]. In 2005, the Sankai Gynecology Study Group used 11 patients and a mathematical model to compare IP and IV carboplatin infusions and demonstrated that a 1-hour infusion of IP carboplatin under normothermic conditions achieves the same 24-hour area under the curve (AUC) in the serum as that with IV administration, but yields an AUC in the peritoneal cavity that is 17 times higher than that obtained from IV administration [7]. This study has not yet been replicated under hyperthermic conditions or with other agents. Some centers use multiple agents simultaneously. Ansaloni investigated the pharmacokinetics of using concomitant cisplatin/paclitaxel for 90 minutes in 13 women with primary or recurrent disease undergoing cytoreductive surgery [25]. Though the approach was feasible and achieved high peritoneal drug concentrations with low systemic exposure, 8 of the 13 patients experienced a grade 3 or higher complication, most of which were hematological. The approach for platinum-resistant patients varies, with some institutions still giving these patients a platinum-based agent and reporting benefit [22]. Head to head comparisons of different chemotherapeutic agents would be necessary to determine the most preferable agent and dosage, and perhaps alternative agents should be considered in the platinum-resistant population.

Open and closed techniques are both safe and feasible. Pilot studies using carbon dioxide for drug circulation, eliminating the need for manual agitation, are also safe and feasible [26]. Fagotti et al also demonstrated that a minimally invasive surgical (MIS) approach to HIPEC treatment in patients with recurrent disease is practical, with minimal complications [27]. Future studies should incorporate comparison of various techniques to determine a standard of care.

IV. The Role of HIPEC in Primary Disease Treatment

The standard of care for treating advanced ovarian cancer in the upfront setting is primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy or neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery [28]. Despite the fact that most patients achieve an initial clinical remission with this approach, there is a need to improve on it as the vast majority subsequently develop recurrent disease. The incorporation of hyperthermic approaches may possibly lead to better results in this population. In a retrospective study of 13 French institutions, Bakrin et al found cytoreductive surgery plus HIPEC in the primary setting yielded a 12-month progression-free survival (PFS) and a 35-month OS [29]. A significantly longer OS of 41.5 months was achieved in patients who were cytoreduced to no visible disease. Ansaloni et al had similar findings showing a significant difference in PFS in patients who were cytoreduced to no visible disease [30]. Studies have shown that HIPEC appears to improve 1-, 2-, 3-, 4-, 5-, and 8-year survival when used in the primary setting, although this has not been proven in a randomized controlled trial [31].

Some centers have even proposed using HIPEC after NACT or for consolidation therapy. A 2014 Spanish review of 87 consecutive patients with ovarian cancer, over half of whom had been treated with NACT, found HIPEC to be associated with a prolonged PFS in all subgroups except those with undifferentiated tumors compared to the control arm of patients who had not received HIPEC [32]. Rettenmaier et al published a report of 37 patients who had been treated with cytoreductive surgery, 6 cycles of postoperative IV carboplatin/paclitaxel, and then consolidation carboplatin-based HIPEC with a planned 12 cycles of maintenance IV paclitaxel [33]. HIPEC was administered within 3 weeks of completing the primary chemotherapy regimen via a GelPort placed in a 4-cm midline infraumbilical incision. They reported premature survival data, with a 13-month (range, 6–19) PFS and a 14-month (range, 6–19) OS, and had no control group.

The randomized, phase 3 Gynecologic Oncology Group (GOG) study 172 reported the longest median OS (66 months) in stage III, optimally debulked patients with ovarian cancer treated with normothermic IP chemotherapy [34]. None of the studies of HIPEC in the primary setting have shown similar survival data. Randomized phase 3 clinical trials including HIPEC are needed to determine whether there is a true role for HIPEC in the upfront setting. Perhaps HIPEC will be most useful in patients who are at high risk for being unable to complete postoperative IP therapy or will be receiving weekly taxol regimens instead. However, studies would need to show that HIPEC would not compromise the ability to receive dose-dense therapy afterwards.

V. The Role of HIPEC in Recurrent Disease Treatment

Several studies have examined the role of HIPEC in the management of patients with recurrent ovarian cancer. Investigators have compared outcomes in patients who received HIPEC during secondary cytoreductive surgery (SCS) with those who only received SCS and postoperative chemotherapy and those who only received IV chemotherapy without SCS.

A 2012 Italian study compared patients with recurrent platinum-sensitive disease treated with SCS and oxaliplatin-based HIPEC with similar patients who had comparable clinical and pathological characteristics who were treated with SCS or systemic chemotherapy over the same time period [35]. They found that the HIPEC cohort did not experience a delay in starting adjuvant chemotherapy, although there was some HIPEC-related toxicity in 35% of the patients. Most notably, they reported that within 2 years, all patients in the control group experienced another recurrence, while only two-thirds of those in the HIPEC group did. The HIPEC group experienced longer secondary responses, and 53% of those patients experienced a longer clinical remission after their recurrence than after their initial treatment. In 2015, this group published their 5- and 7-year survival outcomes for 70 women who were treated with SCS and cisplatin- or oxaliplatin-based HIPEC for recurrent disease [36]. Their findings were consistent with the 2012 report, with greater than 52% of patients experiencing a longer second clinical remission than their first. This is higher than that reported by many chemotherapy trials in a similar population, as the second and subsequent remissions are traditionally shorter than the first [37, 38].

A similarly designed 2013 study from France compared patients who were treated with HIPEC and experienced their first platinum-sensitive recurrence to a randomly extracted matched control group of patients who were not treated with HIPEC but had cytoreductive surgery [39]. However, their patients received systemic chemotherapy prior to SCS +/− HIPEC. Despite the different approach, they also reported significantly improved survival outcomes, with a 75% 4-year survival rate in the HIPEC group compared to 19% in the control group. They also concluded that HIPEC was more useful in earlier recurrences, with patients who had a disease-free interval of less than 2 years experiencing the greatest benefit compared to their control group counterparts [39]. Although both studies included a large number of patients, selection bias and selection criteria represent inherent confounders. This is a common scenario when looking at retrospective studies evaluating surgery in recurrent ovarian cancer, as patients selected to undergo surgery in the recurrent setting predominantly have more favorable patient characteristics.

Hotouras et al performed a systematic review of HIPEC use in recurrent ovarian cancer of 16 studies including more than 11,000 patients, 82% of whom were treated with HIPEC [22]. They found HIPEC to consistently be associated with improved survival, regardless of how the survival rates were reported. Morbidity consistently ranged between 12% and 30%. The complications most frequently associated with HIPEC were hematologic toxicities from the transient bone marrow suppression and renal toxicity [40]. It is difficult to differentiate the surgical complications associated with cytoreductive surgery from those associated with HIPEC. Common complications include ileus, anastomotic leaks, bowel perforations,

fistulas, abscesses, sepsis, bleeding, and wound infections/dehiscences [40]. The OS and PFS rates were similar to those reported in the OCEANS, DESKTOP, and CALYPSO trials; however, given the differences in the trials, direct head to head comparison is not appropriate [22, 41–43].

Spiliotis et al published the first randomized trial of recurrent ovarian cancer and HIPEC [44]. They randomized 120 women with recurrent disease limited to the abdomen undergoing SCS to receive HIPEC or not. They included both platinum-sensitive and -resistant disease, using cisplatin and paclitaxel for the platinum-sensitive patients and a doxorubicin/paclitaxel regimen for the platinum-resistant cohort. All patients were treated by the same surgical team. The OS for the HIPEC group was significantly longer than that of the control group (26.7 vs 13.4 months). As anticipated, the highest OS was observed in patients with complete cytoreduction and HIPEC, but also, the preoperative tumor burden recorded in peritoneal carcinomatosis index (PCI) scores was described as an independent prognostic factor, with a significantly impaired survival in the PCI >15 group. Surprisingly, they did not note a difference in the survival curves between the platinum-sensitive and platinum-resistant cohorts. Classe et al had a similar observation in their retrospective study [45]. Unfortunately, there are several weaknesses in the reporting of this first randomized HIPEC ovarian cancer trial. There is no information regarding PFS, and the authors do not address the median follow-up while showing a high number of censored cases in the Kaplan-Meyer survival curve. There is also no information regarding the postoperative first-line treatment, and complication rates are not addressed. More prospective, randomized data in both the platinum-sensitive and -resistant recurrent populations are needed.

VI. Ongoing Studies and Future Directions

There are 10 ongoing randomized phase 2 and 3 trials recruiting in both primary and recurrent disease, as well as after NACT (Table 1). These studies will certainly provide more useful information about this treatment modality. Four of the ongoing trials are recruiting patients during upfront treatment. The National Cancer Center in Korea is enrolling patients by invitation to be treated with cisplatin-based HIPEC at the time of primary debulking surgery. There are Italian and Dutch trials exploring HIPEC administration at the time of interval debulking after 3 cycles of NACT.

Four clinical trials, including the HORSE (NCT01539785) and CHIPOR (NCT01376752) trials, are recruiting patients who have recurrent disease and are eligible for SCS. Both of the aforementioned studies are multi-institutional randomized trials aimed at assessing the impact of adding HIPEC to complete cytoreductive surgery on PFS and OS, respectively, in recurrent ovarian cancer. CHIPOR hypothesizes that HIPEC will improve the median OS by 12 months. Both trials will use cisplatin-based HIPEC ($75 mg/m^2$) for 60 minutes. Memorial Sloan Kettering Cancer Center has joined with collaborating institutions to also recruit patients with first platinum-sensitive recurrence, but will treat patients with carboplatin-based HIPEC for 90 minutes. Many of these trials will assess similar secondary objectives, such as morbidity, quality of life, and pharmacokinetics [46].

These randomized controlled clinical trials give the field great promise in providing prospective data to determine the benefit and utility of HIPEC in ovarian cancer. Continued exploration is warranted to determine the best agents and protocols to be utilized. Perhaps an international consensus would be helpful to streamline HIPEC training and administration. Future studies should also include cost analysis and quality of life benefit.

The field of gynecologic oncology may eventually evolve to include HIPEC as a routine therapy for primary and/or recurrent ovarian cancer. Until data are available from randomized controlled trials, it is reasonable to further conclude that surgical cytoreduction and HIPEC is a rational, though still investigative, approach in the management of epithelial ovarian cancer, whose use should be employed under the umbrella of Institutional Review Board approved clinical trials.

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Table 1

Phase 2/3 Randomized, Controlled HIPEC Trials

Clinicaltrials.gov Identifier	Sponsor	Condition	Intervention	HIPEC Regimen	Status
NCT02681432	Hospital General de Ciudad Real University of Castilla-La Mancha, Spain	**Primary or recurrent** epithelial ovarian carcinoma (Stage II or higher)	Cytoreductive surgery followed by HIPEC, adjuvant chemotherapy	Paclitaxel 175mg/m^2 for 60 min at 42–43°C	Recruiting
NCT01539785	Catholic University of the Sacred Heart	**Recurrent**, platinum-sensitive ovarian cancer	Secondary cytoreductive surgery followed by HIPEC, adjuvant chemotherapy	Cisplatin 75mg/m^2 for 60 min at 41–42.5°C	Recruiting
NCT01091636	National Cancer Center, Korea	**Primary** ovarian, tubal, and peritoneal cancers (Stage III or higher)	Cytoreductive surgery followed by HIPEC, adjuvant chemotherapy	Cisplatin 75mg/m^2 for 90 min at 41.5°C	Enrolling by invitation
NCT02124421	Mercy Medical Center	**Primary** ovarian, tubal, and peritoneal cancers (Stage III or higher)	Cytoreductive surgery followed by HIPEC, adjuvant chemotherapy	Carboplatin AUC=6	Recruiting
NCT01628380	A.O. Ospedale Papa Giovanni XXIII	Stage IIIC unresectable epithelial tubal/ovarian cancer with partial or complete response after 3 cycles of 1st-line chemotherapy	Interval cytoreductive surgery followed by HIPEC	Cisplatin 100mg/m^2 and Paclitaxel 175mg/m^2 for 90 min at 42°C	Recruiting
NCT00426257	The Netherlands Cancer Institute	Stage III ovarian, peritoneal, or tubal carcinoma patients eligible for interval debulking surgery either following primary chemotherapy or following incomplete primary debulking and chemotherapy	Interval cytoreductive surgery followed by HIPEC	Cisplatin 100mg/m^2	Ongoing, not recruiting
NCT01588964	Catholic University of the Sacred Heart	**Recurrent**, platinum-sensitive ovarian cancer	Secondary cytoreductive surgery followed by HIPEC, adjuvant chemotherapy	Oxaliplatin 460mg/m^2 at 42°C	Completed
NCT01376752	UNICANCER	**Recurrent**, platinum-sensitive ovarian carcinoma with peritoneal disease only after platinum-based second-line chemotherapy	Cytoreductive surgery followed by HIPEC	Cisplatin 75mg/m^2 for 60 min	Recruiting
NCT01767675	Memorial Sloan Kettering Cancer Center	**Recurrent** platinum-sensitive ovarian, tubal, or peritoneal cancer	Secondary cytoreductive surgery followed by HIPEC, adjuvant chemotherapy	Carboplatin 800 mg/m^2 for 90 min at 41–43°C	Recruiting
NCT02567253	University Hospital, Ghent	**Primary or recurrent platinum-sensitive** serous epithelial ovarian or peritoneal carcinoma	Cytoreductive surgery followed by normothermic or hyperthermic IP chemotherapy	Cisplatin 75 or 120 mg/m^2 for 90 min at 37°C or 41°C	Recruiting

Clinicaltrials.gov Identifier	Sponsor	Condition	Intervention	HIPEC Regimen	Status
NCT02328716	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia	Peritoneal carcinomatosis arising from **primary or platinum-sensitive recurrent** ovarian, peritoneal, or tubal carcinoma (Stage III or higher)	Cytoreductive surgery followed by HIPEC	Cisplatin	Ongoing, not recruiting

HIPEC, hyperthermic intraoperative intraperitoneal chemotherapy; AUC, area under the curve