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It's time to warm up to hyperthermic intraperitoneal chemotherapy for patients with ovarian cancer

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Abstract

The peritoneal spread of ovarian cancer makes it a potential target for hyperthermic intraperitoneal chemotherapy (HIPEC). Intraperitoneal delivery exposes the tumor to concentrations of cytotoxic drugs much greater than with intravenous delivery, and *in vitro* studies have also shown that combining hyperthermia and platinum leads to an additive cytotoxic effect. Pharmacokinetic analyses have confirmed very high concentrations of cytotoxic drugs in the peritoneal cavity, with minimal systemic exposure and toxicity.

The majority of historical data evaluating HIPEC in ovarian cancer are based on retrospective research, which included heterogeneous groups of patients and drugs used for HIPEC. Recent publications on the findings of prospective studies, including the first randomized trial in which the only difference in intervention was the addition of HIPEC with cisplatin to interval debulking surgery in stage III patients, have shown a benefit in favor of HIPEC. Yet, a recent prospective study from Korea did not find a benefit.

Opponents of HIPEC have cited higher rates of complications with this approach, yet most of the serious adverse events observed are likely related to the surgery itself, and are comparable to the

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rates reported in studies evaluating cytoreductive surgery without HIPEC. Findings from a recent randomized controlled trial showed no delays in initiation or completion of postoperative chemotherapy in patients treated with HIPEC.

A growing body of evidence is indicating that it might be time to seriously consider HIPEC as a complementary treatment at the time of cytoreductive surgery for patients with advanced-stage ovarian cancer in the setting of an experienced center. Yet, more research is needed to identify the population of patients who gain the most benefit from this therapy.

Keywords

hyperthermic intraperitoneal chemotherapy; HIPEC; ovarian cancer; debulking surgery

Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) administered at the time of cytoreductive surgery has been the subject of discipline-based debates within the oncology community for decades. For the first time, HIPEC was recently included in the National Comprehensive Cancer Network (NCCN) Guidelines, for use in colon cancer [1].

Ovarian cancer is a classic peritoneal malignancy, and many surgical oncologists have proposed the addition of HIPEC to the surgical management of patients with advanced ovarian cancer. This proposal, however, until recently, was based mostly on retrospective data and expert opinions. The current argument for the use of HIPEC in this disease setting is now backed by a larger evidence base, and HIPEC's acceptance is gaining traction. In this overview, we discuss the traditional, current, and future role of HIPEC in the management of patients with ovarian cancer.

Rationale for locoregional chemotherapy in patients with ovarian cancer

In 1978, Dedrick et al. introduced the idea of a peritoneal/blood barrier allowing for high intraperitoneal (IP) doses of chemotherapeutic agents with limited systemic toxicity for peritoneal malignancies [2]. In order for a chemotherapeutic drug to be effective, it needs to penetrate via passive or active transport mechanisms into the cancer cell and/or the nucleus and interact with the substrate (e.g. DNA or disruption of microtubule function) [3].

Local delivery of the cytotoxic drug exposes tumors within the peritoneal cavity to concentrations several times greater than that attained with intravenous (IV) drug administration. There is a major pharmacologic advantage for IP chemotherapy delivery, with improved tumor cell access, prolonged drug exposure, increased dose intensity, slow peritoneal clearance, and the potential to overcome chemoresistance [4].

Pharmacokinetic characteristics play an important role in drug selection for IP drug administration [5–8]. The molecular size of the drug correlates with drug levels in the peritoneal cavity and the plasma. For example, peak peritoneal paclitaxel concentrations exceed plasma concentrations by 1,000-fold and persist in the peritoneal cavity for more than 24 hours due to the large size of the paclitaxel molecule compared with cisplatin; the

latter shows a 12-fold higher concentration in the peritoneal compartment compared with the concentration in serum. The high IP drug concentration may overcome drug resistance by overriding drug efflux and DNA repair mechanisms [3].

IP treatment administered postoperatively with drugs such as cisplatin and paclitaxel (not heated and not delivered in the operating room during the cytoreductive procedure) has been the subject of several randomized clinical trials. Findings from 3 randomized trials evaluating postoperative IP treatment have supported the addition of IP chemotherapy [9–11]. The most recently published phase 3 trial, Gynecologic Oncology Group (GOG) 172, randomly assigned patients—after optimal primary debulking (≤1 cm residual disease) of stage III ovarian, fallopian tube, or peritoneal cancer with postoperative residual tumor <1 cm—to receive either IV paclitaxel 135 mg/m^2 over 24 hours on day 1 and IV cisplatin 75 mg/m^2 on day 2, or IV paclitaxel 135 mg/m^2 over 24 hours on day 1 and IP cisplatin 100 mg/m^2 over 24 hours on day 2 followed by IP paclitaxel 60 mg/m^2 on day 8 of a 3-week cycle. Only 42% of patients randomized to postoperative IV/IP treatment completed all 6 planned postoperative cycles (the others were stopped due to toxicity) and continued with IV treatment only. Despite this, progression-free survival (PFS) and overall survival (OS) was improved with the incorporation of IP treatment. The investigators showed a significantly increased PFS and OS in favor of the IV/IP treatment arm over the IV-only treatment arm (23.8 months vs 18.3 months, respectively [P=0.05]; and 65.6 months vs 49.7 months, respectively [P=0.03]) [11]. Based on these results, the National Cancer Institute issued an alert encouraging the incorporation of IP therapy into the care of women with optimally debulked stage III ovarian cancer in the United States. Longer follow-up data from GOG protocols 114 and 172 were retrospectively analyzed, and the advantage of IP over IV treatment was observed to persist beyond 10 years [12].

The major disadvantages of IP chemotherapy are the increased toxicity and the complex logistical management of patients and their side effects, which have resulted in a general underuse of the IP approach [13, 14]. In GOG 172, 58% of patients discontinued IP therapy due to increased hematologic and gastrointestinal toxicity; inadequate hydration or inadequate antiemetic therapy; or IP port complications, including obstruction, leakage, and infection. For these reasons, in the most recent IP study, the GOG 252 trial, a modified outpatient IP treatment regimen was introduced:

- Arm 1: IV carboplatin AUC (area under the curve) 6/IV weekly paclitaxel at 80 mg/m^2
- Arm 2: IP carboplatin AUC 6/IV weekly paclitaxel at 80 mg/m^2
- Arm 3: IV paclitaxel at 135 mg/m^2 on day 1/IP cisplatin at 75 mg/m^2 on day 2/IP paclitaxel at 60 mg/m^2 on day 8.

In addition, patients in each arm received IV bevacizumab at 15 mg/kg with cycles 2 through 6 of chemotherapy and then as maintenance for cycles 7 through 22.

GOG 252 failed to show a PFS advantage with IP cisplatin/IP paclitaxel or IP carboplatin over dose-dense IV paclitaxel and carboplatin. Differences in trial design included the use of bevacizumab in all arms of the study and the modified outpatient IP regimen, as well as the

protocol-specific use of computed tomography (CT) scanning in the surveillance setting. Longer follow-up time is necessary to evaluate OS.

Independent of whether the outpatient protocol will have a comparable OS efficacy to that of the GOG 172 regimen, postoperative IP treatment will still be challenging for healthcare providers due to higher complication rates, the need for additional homecare to ensure adequate IV hydration, longer treatment times, and intensified nursing involvement. These factors remain the major limitations of IP chemotherapy as the standard of care and have resulted in a general underuse.

Rationale for HIPEC

HIPEC differs distinctly from postoperative IP delivery in that it is a single treatment of intraoperative chemotherapy at the time of cytoreductive surgery for peritoneal surface malignancies [15, 16]. The chemotherapeutic agent is typically diluted in normal saline and warmed to 42°C before being introduced into the peritoneal cavity. The solution is either introduced via the open coliseum technique or the closed abdomen technique. Although each HIPEC perfusion technique has its own advantages and shortcomings, no controlled prospective studies have compared the different methods of administration [17]. Some data suggest that the closed technique results in a more stable IP temperature. However, there is not enough scientific evidence to favor one technique over the other. The duration of perfusion varies from 60 minutes to 120 minutes, and at the completion of administration, the perfusate is usually drained and the abdominal cavity is irrigated.

The precise cytotoxic mechanisms associated with hyperthermia require further elucidation. Temperatures in the range of 42–45°C have shown to cause lethal cell damage [18]. Alterations in the cell membrane and nucleus, protein denaturation, and changes in calcium permeability are thought to be responsible for cytotoxic effects. Although hyperthermia may affect normal tissues as well, the heat effect disproportionately affects hypoxic tumor cells due to the relative poor perfusion and acidotic state [19]. Hyperthermia also appears to increase sensitivity to chemotherapeutic agents, especially cisplatin, in both platinum-sensitive and platinum-resistant ovarian cancer cell lines [19]. The increased cytotoxic effect is based on enhanced intracellular drug accumulation and DNA adduct formation. 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 [20–22].

For several reasons, there is interest for combining surgical cytoreduction and HIPEC in the management of ovarian cancer whose natural history remains localized to the peritoneal cavity:

a. Postoperative IP chemotherapy trials in patients with ovarian cancer have shown a survival benefit in favor of IP regimens despite a significant proportion of patients not completing all 6 planned IP cycles, suggesting a survival benefit for patients who receive fewer cycles, possibly just a single administration [9–11].

b. By giving the chemotherapy intraoperatively, barriers of postoperative adhesions can be avoided. Intraoperatively, the chemotherapy can be delivered under highly standardized procedures and the perfusate can be drained from the peritoneal cavity.

c. There is no interval between cytoreduction and chemotherapy. The cytotoxic therapy is applied at the time of surgery, without delay [23, 24].

d. Hyperthermia alone has been associated with cytotoxic effects. In addition, hyperthermia has been shown to increase the cytotoxic effect of many chemotherapeutic agents by increasing DNA crosslinking and tumor penetration [25–27].

Phase 1/2; studies, pharmacokinetics, toxicity, morbidity, and mortality

A number of phase 1/2; studies in both primary and recurrent disease settings have been performed. Zivanovic et al. assessed dose-escalated cisplatin administered as HIPEC during secondary cytoreductive surgery in 12 patients with platinum-sensitive recurrent ovarian cancer [28]. The median peritoneal cancer index (PCI) was 14.5, and all but 4 patients had their disease resected to 2.5 mm or less. The median operative time, including the 90-minute HIPEC procedure, was 463 minutes. No intestinal anastomotic leak, no postoperative thromboembolic events, or grade 2 or higher hematologic toxicity were observed. There were no perioperative deaths or grade 4 adverse events. One patient's postoperative course was complicated by a grade 3 acute renal injury, which was considered a dose-limiting toxicity. Pharmacokinetic measurements showed high IP doses of cisplatin and low systemic exposure. The IP-plasma platinum AUC ratio during the perfusion was 19.5 for 100 mg/m^2, confirming the favorable pharmacokinetic properties of cisplatin. The limited rate of observed chemotherapy-related side effects in this study was confirmed by the very low systemic exposure of cisplatin measured during and after HIPEC, underlining the pharmacologic advantage of cisplatin administered as HIPEC. Tumor samples before and after HIPEC were frozen for detection of cisplatin-induced intra-strand crosslinks in nuclear DNA and were confirmed in tumor biopsies after 90 minutes of HIPEC. The addition of HIPEC did not compromise the ability to postoperatively administer standard systemic carboplatin-based combination chemotherapy. Paclitaxel was recently investigated in the setting of HIPEC. De Bree et al. performed a pharmacokinetic study on 13 patients administered 175 mg/m^2 paclitaxel over 2 hours [29]. The IP-plasma AUC ratio was 1462 for the 2-hour HIPEC duration and 366 for the total 5-day study period. Cytotoxic drug concentrations were detected in peritoneal fluid for a mean period of 2.7 days, despite drainage of the drug solution after 2 hours of treatment. The delivery of paclitaxel 175 mg/m^2 showed an acceptable morbidity rate of 38% (all complications), with no postoperative deaths. It should be noted that this study included patients with primary and recurrent disease, as well as those with persistent disease. All but 3 women had a cytoreduction to 5mm or less.

Ansaloni et al. evaluated 11 patients who received combination cisplatin and paclitaxel as HIPEC [30]. Cisplatin was administered at a dose of 100 mg/m^2 and paclitaxel at a dose of 175 mg/m^2 over 90 minutes. In the study, superficial penetration of paclitaxel into the tissue

was seen with ionization imaging mass spectrometry. Grade 3–4 surgical complications were recorded in 4 patients. Five patients experienced grade 3 and 2 patients experienced grade 4 hematological complications (thrombocytopenia and anemia). There were no mortalities.

The most recent phase I HIPEC trial was presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting [31]. Thirty women who underwent complete or optimal cytoreduction at the time of primary or interval debulking surgery for advanced-stage disease were treated with HIPEC using carboplatin. The maximum tolerated dose was determined to be 1,115 mg/m^2. Grade 3 or higher complications occurred in 50% of patients, with anemia the most frequent (10%); there was 1 death.

Retrospective Studies

The majority of data evaluating HIPEC in patients with ovarian cancer are based on retrospective research. Using PubMed, we performed a systematic review of retrospective studies specific ovarian cancer and HIPEC use that included at least 30 patients and were published from 2012 on. Twelve retrospective studies reporting on the use of HIPEC for advanced-stage ovarian cancer, both in the upfront [32–36] and recurrent disease setting [32, 37–39] for platinum-sensitive [34, 35, 40, 41] or -resistant disease, were included (Table 1) [32, 34–44]. In addition to their retrospective nature, these studies include heterogeneous groups of patients and drugs. The greatest variation is seen in the chemotherapy agents used, with single-agent platinum and single-agent paclitaxel being the most common, followed by combination therapies. Even within a single study, variation in agents and doses was common. The surgical effort also varied from study to study, with as many as 10–20% of patients having residual macroscopic disease, with an original median PCI of 7–8.

PFS for patients with primary advanced-stage ovarian cancer treated with HIPEC ranges from 12 [32] to 24 months [35], and OS ranges from 42 [32] to 57 months [35]. PFS in patients with recurrent disease ranges from 11 [37] to 27 months [44], and OS ranges from 28 to 63 months [44]. In one of the largest retrospective studies in persistent and recurrent ovarian cancer, Bakrin et al. described survival and morbidity in 246 patients over a period of 17 years. The rate of morbidity was an acceptable 12%, and the median OS was 49 months. Patients with platinum-resistant and platinum-sensitive disease were included [33]. Interestingly, two studies found no difference in survival between platinum-sensitive and -resistant recurrences treated with HIPEC [32, 38], while one study observed improved survival for platinum-sensitive disease. The last study, however, used 12 months, instead of the usual 6 months, to define platinum sensitivity. While the favorable outcomes of patients with platinum-resistant disease are encouraging, they need to be interpreted with caution, as the surgical criteria in these retrospective studies were likely subject to selection bias.

Two studies compared the use of HIPEC in patients with a platinum-sensitive recurrence to controls. One found that fewer patients treated with HIPEC recurred (66% versus 100%, P=0.001) or died from disease (23% versus 62%, P=0.003), while the other found no significant difference in survival (the 3-year PFS rate was 45% with HIPEC compared with 23% with surgery alone, P=0.078). Results from the only study that compared HIPEC with

standard care in the upfront setting showed that the 3-year PFS rate was higher with HIPEC compared to that of the control group (63% versus 18%, $P<0.01$).

Reported rates of serious (grade 3 or higher) complications range from 8.6% to 35.7%, while the rate of 30-day mortality ranges from a reported 0% to 7.1%. The reported rates of major complications are comparable to other large retrospective studies evaluating surgical complication after cytoreductive surgery without the use of HIPEC [45, 46].

Surgical outcomes reported in multiple retrospective studies mimic those of studies without the use of HIPEC, suggesting the safety and feasibility of this approach in centers with expertise. At the same time, survival outcomes are difficult to interpret outside the setting of a randomized trial. Multiple retrospective studies in patients selected to undergo cytoreductive surgery without HIPEC have reported outcomes similar to or not inferior to those of many studies that include HIPEC [47–53].

Prospective Studies

A single-institution randomized phase 3 trial comparing conventional secondary cytoreductive surgery with or without HIPEC in patients with recurrent ovarian cancer was published in 2015 [54]. The study included 120 patients with both platinum-sensitive and platinum-resistant disease, with approximately 50% in each arm having a PCI of 10 or higher. Cisplatin 100 mg/m^2; and paclitaxel 175 mg/m^2; were administered to patients with platinum-sensitive disease, and doxorubicin 35 mg/m² and paclitaxel 175 mg/m^2; or mitomycin 15 mg/m^2; were administered to patients with platinum-resistant disease. The authors reported a mean survival of 27 months for patients randomized to HIPEC versus 13 months for patients in the standard group, with the greatest effect seen in patients with platinum-resistant disease. The validity of the study has been contested due to significant shortcomings in trial design, the study's preoperative randomization process, the inclusion of heterogenous patient cohorts and chemotherapeutic regimens, and a lack of specification of postoperative chemotherapy and follow-up [55, 56].

More recently, van Driel et al. published the first randomized trial evaluating the use of HIPEC with cisplatin at the time of optimal interval debulking surgery for patients with stage III ovarian cancer who had undergone neoadjuvant IV chemotherapy [57]. In the study, 245 patients who had at least stable disease after 3 cycles of IV neoadjuvant paclitaxel and carboplatin chemotherapy were randomly assigned to undergo interval debulking surgery with or without HIPEC with cisplatin at a dose of 100mg/m^2;. Randomization was performed at the time of surgery after intraoperative assessment of resectability to no visible or minimal residual disease measuring 10 mm or less in greatest diameter. Three additional cycles of carboplatin and paclitaxel were administered postoperatively. The median PFS, which was the primary endpoint, was 10.7 months in patients in the standard arm versus 14.2 months in patients who were treated with HIPEC (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.50 to 0.87; $P=0.003$). At the time of analysis, 44% of patients were alive, with a significant improvement in median OS favoring HIPEC (45.7 vs. 33.9 months; HR, 0.67; 95% CI, 0.48 to 0.94; $P=0.02$). The number of patients with grade 3–4 adverse events was similar between treatment arms (27% vs 25%; $P=0.76$). There was no

delay in postoperative chemotherapy treatment and no compromise in completing an additional 3 cycles of chemotherapy in the postoperative setting in patients who received HIPEC. In addition, there was no difference in health-related quality of life. This was the first reported randomized trial in which the only intervention that differed between groups was the use of a single, 90-minute perfusion of cisplatin after surgical cytoreduction. The dose of cisplatin was determined at 100 mg/m^2, which had been established in previous phase 1/2; and multiple retrospective studies. Protocol-specific standardized surveillance measures, including defined CA-125 measurements and CT scans, were used to assess the primary endpoint of PFS. Safety assessments were included and adequately addressed. In addition, the median PFS and OS in the control group was reproducible and identical to previously reported outcomes from randomized clinical trials that included patients with similar inclusion criteria. The study did not address the higher costs of treatment in the HIPEC arm, which were due to longer operating room (OR) and hospitalization times and higher rates of diverting ostomies. This is an area that needs further evaluation.

Yet, this study is not without limitations. A lot of concern has been expressed regarding the exclusion of stage IV patients and the impact this had on the patient population studied. Looking at our own center data, approximately 50% of women presenting with advanced disease are treated with NACT, for surgical or medical reasons. Of the women who undergo interval surgery, approximately 60% have stage IV disease, and complete or optimal resection is achieved in 90%. By excluding stage IV NACT patients, the study randomized approximately 23% of presenting women. There is also concern regarding the low recruitment at certain centers, but this can be said about any multi-center trial, making surgical effort the most challenging to standardize.

The results of a Korean randomized trial were presented at the 2017 ASCO Annual Meeting [58]. The trial randomized 184 women with stage III or IV disease to surgery with or without HIPEC at the time of primary or interval debulking surgery (39.1%). There was no difference in either PFS or OS between the two groups, even when analyzed separately by debulking type. The most common complications for the HIPEC group were anemia (67.4%) and elevated creatinine (15.2%); there were no deaths.

Discussion

Locoregional treatment strategies provide decreased systemic toxicity and a high pharmacologic advantage for tumors confined to a single organ or body cavity. While IP chemotherapy for patients with advanced ovarian cancer has been accepted as part of standard of care, HIPEC administered at the time of cytoreductive surgery remains debatable [55, 59–61]. Safety is a major concern for some gynecologic oncologists who fear that patients undergoing surgery with HIPEC will be too sick to subsequently proceed with standard and proven effective postoperative chemotherapy. In addition, delays in postoperative treatment or compromise of the number of chemotherapy cycles are associated with inferior survival. Furthermore, the rejection of HIPEC falls under the general critique of locoregional therapy for patients with ovarian cancer, traditionally by the same groups who have not been convinced by data supporting postoperative IP treatment [62, 63].

Ten years ago, there was not enough robust evidence to support the role of HIPEC in patients with ovarian cancer, but now we have promising data from multiple phase 1/2; trials and sizable retrospective studies. The incorporation of pharmacokinetic analyses into HIPEC studies has confirmed very high concentrations of chemotherapeutic agents in the peritoneal cavity, with minimal systemic exposure and toxicity. Tissue penetration and DNA adduct formation of platinum and taxane-based compounds have been confirmed, and the safety of cisplatin at a dose of 100 mg/m^2; has been reproduced in multiple settings. There are now 2 randomized controlled trials evaluating the use of HIPEC in the upfront setting, although in different patient populations. One showed a benefit of HIPEC and one did not, highlighting the need for further high-quality research in this area.

The vast majority of adverse events observed in experienced centers is related to the surgical procedure itself, with rates similar to those reported in studies evaluating the role of cytoreductive surgery without HIPEC. A recently published randomized trial confirmed the safety of the approach, which is important considering the longer OR time and the addition of a chemotherapeutic agent during surgery. As reported in other studies, there was no delay in the initiation of postoperative chemotherapy and no compromise in completing chemotherapy in the postoperative setting. From the multiple published studies, it is clear that cytoreductive surgery and HIPEC with cisplatin is safe when performed in experienced centers. Ongoing concerns about the safety and feasibility of HIPEC appear outdated and should be put into perspective, considering our acceptance of significant toxicities with novel systemic therapies [64–68].

Future Direction

With this accumulation of prospective data over the past decade, it is difficult to disregard the future of HIPEC as a treatment option for patients with ovarian cancer. The results of the recently published randomized trial demonstrating the clinical efficacy of 100 mg/m^2; cisplatin over 90 minutes with HIPEC during interval cytoreductive surgery are encouraging, but legitimate questions about how to best apply this technique in routine care remain.

We must first address the question of which component of HIPEC is associated with the improved outcomes. Is it the dose effect of the drug, which within 90 minutes needs to penetrate into the remaining tumor cells either via active or passive transport mechanisms, where it then interacts with its substrate, interfering with cell division and activating apoptosis, at the same time escaping efflux and DNA repair mechanisms of the tumor cell? Is it the hyperthermia, which alone has been shown to have cytotoxic effects by damaging proteins and cell structures? To what extent does hyperthermia facilitate and enhance the effect of certain drugs? Is it the early use of chemotherapy in the OR? In hopes of answering some of these questions, a Belgian group is comparing HIPEC to normothermic (37°C) intraoperative IP cisplatin, given at 2 concentrations for each, at the time of primary cytoreductive surgery (). A study out of Maryland is comparing HIPEC using carboplatin at the time of primary surgery to postoperative IP cisplatin/paclitaxel chemotherapy ().

Next, we must figure out the role of patient selection in determining which patients will benefit from HIPEC. Is every patient fit for cytoreductive surgery also fit for HIPEC or do

we have to exclude patients based on co-morbidities (e.g., preexisting renal conditions, diabetes)? The majority of HIPEC studies are performed in patients with a good performance status; however, we must acknowledge that this is a highly select group of patients.

Another important factor to consider is the role of neoadjuvant chemotherapy versus primary debulking surgery in patients who will undergo HIPEC. The patients included in the recently published randomized study by van Driel et al. were patients undergoing neoadjuvant chemotherapy. While study results showed an increase in PFS and OS in favor of HIPEC, best reported survival outcomes for patients with ovarian cancer are observed when treated with primary surgery followed by chemotherapy [69, 70]. Thus, the results of the van Driel trial should not be interpreted in a way that leads to more patients being triaged to neoadjuvant chemotherapy [71]. A collaborative study out of Germany and Italy is focused on answering a similar question about the use of HIPEC during interval surgery, including both stage III and IV patients ().

Lastly, can the positive results seen with HIPEC be expected in less-experienced centers? And how much of the favorable toxicity profile depends on experience? It is likely that clinical experience will be an important driver of outcomes in this setting.

A new emerging method of delivering IP chemotherapy, pressurized IP aerosol chemotherapy (PIPAC), has recently been studied in ovarian cancer. The principle of PIPAC is based on the observation that delivery of chemotherapy under pressure increases uptake by the tumor, which in turn allows for decreased doses of chemotherapy [72]. Tempfer et al. reported the outcomes of 18 women treated with PIPAC for recurrent platinum-resistant ovarian cancer using cisplatin and doxorubicin [73]. In 8 women, PIPAC was combined with surgical resection. Objective tumor response was seen in 6 women, and grade 2 or higher adverse events in 5. There were no deaths. The decreased dose used in PIPAC makes it an attractive option for older patients [72], yet further research is needed to evaluate the potential role of PIPAC in this patient population. HIPEC is usually reserved for healthy patients, with most studies enrolling only patients with a good performance status.

Conclusion

Gynecologic oncologists now have a large pool of evidence to support the use of HIPEC and incorporate HIPEC into novel clinical trial designs. In an evolving environment of molecular diagnostics, novel targeted therapies and an ongoing underuse of postoperative IP treatment, HIPEC may serve as a complementary treatment at the time of cytoreductive surgery and may improve the outcomes of women with ovarian cancer. Or with more data, HIPEC in ovarian cancer could follow the same trajectory as for colorectal cancer, with recent data suggesting that HIPEC does not improve survival [74]. But at this time, it is still unclear which patients with ovarian cancer will benefit most from HIPEC.

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Highlights

- HIPEC eliminates the time interval between cytoreduction and chemotherapy
- HIPEC at interval debulking surgery has shown a progression-free survival advantage
- Multiple studies show HIPEC is safe when performed at an expert center

Table 1

. Retrospective studies reporting on the use of HIPEC for advanced-stage ovarian cancer

First Author	Year	N	Setting	HIPEC Drug	PFS	OS	Serious Complications	Mortality Rate	Outcome
Deraco	2012	56	1st recur -PS and PR	Cisplatin+doxorubicin, cisplatin+mitomycin	10.8mos	25.7mos	26.3%	5.3%	
Fagotti	2012	30	1st recur -PS	Oxaliplatin	26mos cases vs 15mos cntr (p=0.004)		34.8%	**0%**	Recur 67% HIPEC vs 100% control (p=0.001), Death 23% HIPEC vs 62% control (p=0.003)
Bakrin	2013	92	Primary	Cisplatin±doxorubicin, ± mitomycin, oxaliplatin	11.8mos	42mos	31.3%	0.8%	No difference in PS and PR survival
		473	1st recur -PS and PR			45.7mos			
Bakrin	2013	36	Primary	Oxaliplatin, mitomycin ± platinum	16.7mos	3yr: 71.5%	20.6%	5.6%	
Robella	2014	70	1st recur			28mos	35.7%	7.1%	
Cascale-Campos	2014	52	Primary	Paclitaxel	3 yr: 63%				Compared to no HIPEC 3yr PFS: 18% (p<0.01)
Classe	2015	314	1st recur -PS and PR	Cisplatin ± combination	5yr: 14%	5yr: 38%	30.9%	1%	No difference in PS and PR survival
Cascale-Campos	2015	32	1st recur -PS	Paclitaxel	3yr: 45%		21%		Compared to noHIPEC3yr PFS: 23% (p=0.078)
Coccolini	2015	30	Primary	Cisplatin + paclitaxel	12.5mos	32.9mos	35.2%	5.6%	
		24	1st recur - PS						
Petrillo	2016	70	1st recur -PS	Oxaliplatin, cisplatin	27mos	63mos	8.6%	0%	
Munoz-Casares	2016	124	Primary	Paclitaxel, cisplatin	24mos	57mos	13.8%	1.4%	
		94	1st recur		19mos	55mos			
Di Giorgio	2017	226	Primary		16.6mos	52.4mos	17.4%	2.5%	PS better survival than PR (used 12 mo to define PS)
		285	1st recur -PS and PR						

HIPEC, hyperthermic intraperitoneal chemotherapy; PFS, progression-free survival; OS, overall survival; PS, platinum sensitive; PR, platinum resistant