Introducing Hyperthermic Intraperitoneal Chemotherapy into Gynecological Oncology Practice – Feasibility and Safety Considerations: Single-Center Experience

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that certain considerations and precautions are taken into account during its introduction to guarantee a proper and safe operating sequence.

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Introduction

Epithelial ovarian cancer (EOC) is the fourth most common cancer in women and the leading cause of death from a gynecological malignancy. Annually 125,000 women die due to this malignancy worldwide [1]. As the initial symptoms of this disease are nonspecific, the majority of women are diagnosed at an advanced stage, typically presenting with peritoneal metastases [2]. A combination of surgical cytoreduction and platinum-paclitaxel chemotherapy remains the standard of therapy for advanced ovarian cancer [3–5]. The alternative approach of neoadjuvant treatment has been shown to be equivalent in achieving complete elimination of all visible disease, at least in certain subgroups [4, 6–8]. In the majority of patients, the natural history of advanced-stage ovarian cancer typically consists of initial clinical remission after primary treatment followed by early or late recurrence, leading to recurrent episodes of bowel obstruction, tumor cachexia and death [9]. Prevention or delay of recurrence or progression is the major focus in the management of ovarian cancer. To improve the long-term outcome of women with advanced EOC, there is need for new therapeutic strategies. As EOC is a chemo-sensitive disease and stays within the peritoneal cavity for a long periods during its natural history, Dedrick and colleagues [10] published a theoretical model-
ling study supporting the use of intraperitoneal drug delivery as a management strategy for ovarian cancer. The study predicted a major pharmacological advantage for intraperitoneal therapy with improved tumor cell access, longer half-life in the peritoneal compartment, increased dose intensity, and slow peritoneal clearance, so reaching effective levels of systemic exposure for longer periods of time. Several phase III trials then explored the clinical utility of postoperative intraperitoneal therapy following maximal cytoreductive surgery (CS) of advanced ovarian cancer [5, 11–13]. In 2006, based on the results of these randomized phase III trials, the National Cancer Institute (NCI) announced that a combination of intravenously and intraperitoneally administered chemotherapy conveys a significant survival benefit among women with optimally debulked EOC, compared to intravenous administration alone. Despite the NCI announcement, this treatment has not yet been established in clinical practice, mainly because of higher toxicity rates, the high rate of discontinuation and technical complexity. The perioperative administration of intraperitoneal chemotherapy has various advantages over standard intraperitoneal therapy and may help the intraperitoneal administration of cytotoxic agents become increasingly accepted. A locoregional treatment option is the intraoperative combination of CS with hyperthermic intraperitoneal chemotherapy (HIPEC), which allows administering chemotherapy before postoperative adhesions can develop and obstruct the homogenous distribution of the perfusate [14]. Chemotherapy is thus applied not only when the tumor burden is at its lowest, but many days earlier than the time that postoperative chemotherapy is usually given. Complications related to intraperitoneal chemotherapy, such as difficulties associated with the use of port systems, are avoided and theoretically there is the benefit of delivering high concentration of chemotherapy to the tumor without increasing systemic toxicity. The role of HIPEC in the treatment of peritoneal surface malignancies is evolving, and there has been a lot of experience with this complex treatment strategy in solid tumors such as peritoneal metastasized colorectal cancer and pseudomyxoma peritonei [15–17]. The rationale for this approach, besides the optimal distribution, is the tumoricidal effect of hyperthermia [18]. Hyperthermia increases the cytotoxicity of many chemotherapeutic agents in human cell cultures and animal models [11, 19, 20], and enhances the drug penetration into peritoneal tumor implants [21, 22]. Based on these data, an increasing number of centers are starting to implement this therapeutic approach in the treatment of EOC. Unfortunately, currently there is no evidence from prospective trials to objectively confirm an overall survival benefit associated with surgical resection in combination with HIPEC. A few phase I/II studies and mostly retrospective institutional experiences have suggested the feasibility of employing an intraoperative regional therapeutic approach with cisplatin administered as HIPEC. However, data are inconsistent with regards to maximum tolerated dose (MTD) and morbidity, and results are weakened by the inclusion of heterogeneous patient cohorts in both the primary and the recurrent setting. We therefore initiated a phase I study of HIPEC with cisplatin in patients with platinum-sensitive recurrent EOC. The purpose of this study was to determine the safety, feasibility, MTD, pharmacokinetics and pharmacodynamics of cisplatin administered as HIPEC in patients undergoing secondary CS. The data from this study have been published [23] and prove the feasibility of this approach. In the process of introducing HIPEC into practice, several considerations and precautions regarding the perioperative management in the setting of a multidisciplinary approach had to be taken into account. HIPEC will presumably soon be applied in primary treatment of advanced ovarian cancer, so clinical know-how and expertise is needed in gynecological oncology centers. This paper emphasizes the perioperative implications, precautions and safety requirements for introducing HIPEC into gynecological oncology practice.

**Methods and Results**

In the initiation phase for HIPEC, several points of caution had to be considered. To address all safety concerns with this treatment modality and before initiation of HIPEC into practice, a multidisciplinary HIPEC competence team including anesthesiologists, medical oncologists, pharmacologists, surgeons, operating room (OR) and intensive care unit (ICU) staff, and nurses was established. The competence team was responsible for developing standard operating procedures and reviewing existing institutional policies and guidelines pertinent to patient selection, operating room scheduling, chemotherapy administration, handling of cytotoxic agents, processing of surgical equipment, exposure to cytotoxic agents, handling of specimen, handling of contaminated body fluid and disposal of cytotoxic waste. In addition, the team was responsible for reviewing existing anesthesiological policies pertinent to CS and hyperthermia. As part of developing standard operating procedures for HIPEC, delegates of the competence team also visited a center that has extensive expertise with HIPEC, which proved to be a very valuable experience.

**Patient Selection**

Patients selected to undergo CS with HIPEC should have an adequate performance status (Karnofsky Index > 70%) with unimpaired hematological, renal and liver functions. Furthermore, there should be no serious limitations as a result of concomitant diseases. Care should be taken to rule out any chemotherapy-relevant preoperative toxicity that may interfere with the locally administered chemotherapeutic agent. In the case of cisplatin, special attention should be paid to any pre-existing renal or neurological impairment. An important aspect in the setting of EOC is the ability to resect all visible tumors. Therefore, predicting which patients can or cannot undergo complete cytoreduction represents a crucial decision in the management of these patients [24–26]. For the purpose of our study, we used the prospectively validated AGO (Arbeitsgemeinschaft Gynäkologische Onkologie; German Society of Gynecological Oncology) score for the operability of patients with recurrent EOC developed by Harter et al. [27]. Resectability was
assumed if 3 factors were present: (1) complete resection at first surgery, (2) good performance status, and (3) ascites less than 500 ml. Imaging studies such as CT scans were also reviewed regarding resectability [24, 28]. The preoperative assessment of whether a complete cytoreduction was possible and the final decision on whether a patient should be offered HIPEC was made by an interdisciplinary panel of physicians who were part of the competence team.

Preoperative Management

Scheduling of the intervention was essential in the initial period to guarantee the availability of the members of the competence team and a constant composition of the surgical team, including all OR staff at the operating table and within the OR. Operations were planned towards the beginning of the week to assure a full staff in the early postoperative period. At our institution, 1 OR was reserved without time limitations, as the time period can differ widely depending on the extent of the CS. When a patient was referred, preoperative assessment including physical examinations, blood tests and further diagnostic tests depending on existing comorbidities were performed. For postoperative monitoring, a transfer of the patient to the ICU was planned in advance. Patients were given heparin as an anticoagulant and wore compression stockings. The dose of the chemotherapeutic agent was calculated from the current weight (body surface area, BSA) of the patient, and ordered from the clinic pharmacy, together with antiemetic medications.

Anesthesiology

The team of anesthesiologists and nurses, as well as the ICU staff were involved in the process at a very early stage, as there were safety concerns about patient management throughout and after the procedure. It was essential to find sufficient team members to build up experience rapidly and efficiently and to assure the availability of staff and the sharing of knowledge and skills. At our center we appointed 2 senior anesthesiologists experienced in anesthesia for abdominal surgery, advanced hemodynamic monitoring and transesophageal echocardiography (TEE). These anesthesiologists trained and supervised a core staff of 3 junior residents. As at least 1 senior and 1 junior team member must be available and since the procedure may involve 12 h of net operating and perfusion time, operations need to be scheduled well in advance.

Preoperative Evaluation

All patients scheduled for HIPEC underwent preoperative evaluation by an anesthesiologist trained for HIPEC. The capacity of a patient to compensate for hemodynamic perturbations during HIPEC, which could lead to severe cardiocirculatory changes, had to be assessed carefully. Other than that, preoperative evaluation was largely equivalent to that before extensive CS. This has recently been thoroughly reviewed [29]. Informed consent included that for our institutional standards for abdominal surgery including thoracic epidural anesthesia, and for advanced hemodynamic monitoring including TEE and the postoperative transfer to an ICU.

General Anesthesia

There are only limited data on the hemodynamic reaction of patients to HIPEC after prolonged and extensive CS, but several authors have described a hyperdynamic circulatory state [30–32]. This mandates a careful intraoperative management, especially in the context of substantial fluid and blood loss that can occur during the sometimes complex and long interventions. There is an extensive body of literature to support the use of a goal-directed protocol for major surgery (reviewed in [33]), thus using one of the suggested protocols is highly recommended. In our center, we use a management based on stroke volume derived from calibrated pulse contour analysis in combination with volumetric parameters derived from transpulmonary thermodilution (TPTD). Transpulmonary measurements are taken every 30–60 min during CS, depending on hemodynamic stability, and every 15 min during HIPEC, although during HIPEC thermal stability can be an issue. It can become necessary to ignore the respective error on the TPTD device and visually check for absence of recirculating cold indicator. We titrate fluids and, if necessary, add catecholamines to achieve optimized cardiac output while maintaining normovolemia. We do not advocate hypervolemia, as observed in one study [31]. Using this strategy, we have encountered no sustained adverse hemodynamic reaction to HIPEC. Urine production is monitored with a standard meter. It should be checked every 15 min during HIPEC, and the tube ‘milked’ to avoid air locks. Urine production during HIPEC is crucial and should be held above 1 ml/kg/h to avoid cisplatin–induced nephrotoxicity. In our experience, with adequate fluid therapy prior to HIPEC, this is achieved in most patients without the use of diuretics. Before HIPEC, body temperature is allowed to drop to 35 °C unless complications arise from hypothermia such as impaired coagulation. However, it is necessary to achieve a mild hypothermic state before initiation of HIPEC to avoid severe hyperthermia during perfusion. With the institutional perfusion regimen (perfusion temperature 42°–43° C for 90 min), 35.0–35.5 °C is a reasonable starting point. Figure 1 displays the changes in blood temperature during...
debunking and HIPEC. Bladder temperature cannot be used during HIPEC, and blood temperature is preferable to esophageal temperature because it responds quicker; however, it depends on a specific device such as a TPTD catheter and monitor. Hypothermia is easily achieved by refraining from active warming and using fluids at ambient temperature. So far, in our institution no active cooling has been necessary, a finding confirmed by other centers. During HIPEC, it is essential to maintain complete neuromuscular relaxation to allow even and constant flow of the perfusate throughout the entire abdominal cavity. Before implementation of HIPEC, increased abdominal pressure has been a concern, especially as the surgical team chose a closed technique. However, using a gastric pressure probe, we did not encounter elevation of the intragastric pressure above 15 mmHg. For postoperative analgesia we inserted epidural catheters preoperatively according to national guidelines for neuraxial techniques. There was some concern about the use of epidural anesthesia [34, 35] in HIPEC, but recently safety has been demonstrated in a retrospective study, although the sample size was small [36]. Despite some evidence that the intraproductive use of epidural analgesia might be associated with a lower recurrence rate of cancer [37], we did not induce intraoperative epidural analgesia due to an occasional detrimental effect on hemodynamics [38]. Postoperatively, all patients were transferred to the ICU, where the monitoring including TEE continued.

**CS and HIPEC**

Due to the duration of surgical procedure and the additional 90 min of HIPEC, it is important to assure correct positioning of the patient to avoid a nerve injury. The aim of optimal cytoreduction is the complete removal of all visible disease. The importance of this cytoreduction is confirmed by multiple retrospective studies demonstrating that the extent of residual tumor inversely correlates with survival time [24, 25, 39]. The dimension of surgical resection, especially in the case of recurrent disease, is technically demanding and requires a broad surgical knowledge including that of non-gynecological upper abdominal procedures. In consideration of the upcoming HIPEC, the surgical team should also decide if a terminal colostomy is necessary to avoid anastomotic leakages. Early recognition of severe complications as the intestinal perforation, anastomotic leakage, pancreatitis, pancreatic fistula or prolonged ileus is also essential. The surgical team has gained experience in the surgical procedures and the management of the postoperative complications, leading to a reduction in intraoperative surgical complications, especially during the performance of extensive upper abdominal procedures. In addition, the arrangements for carrying out HIPEC are now faster and more routine, which has helped to decrease operating time. In multivariate analyses of the largest reported series of HIPEC in ovarian cancer, the effectiveness of carcinomatosis, the radicality of CS, the duration of the total procedure, the extent of peritoneal resection and the number of anastomosis have been independent risk factors for morbidity [40]. In our institution unstable intraoperative hemodynamic conditions or a malfunction of the HIPEC machine have so far been the only limitations for performing HIPEC, while the number of anastomosis or pancreatic tail resection represented no contraindication for HIPEC.

At the end of cytoreduction and 30 min before starting the HIPEC it is mandatory that the anesthesiologist administers the antiemetic medication to prevent nausea induced by cisplatin. The antiemetic prophylaxis consists of the corticosteroid dexamethasone, a 5-HT3 receptor antagonist ondansetron and the neurokinin-1 (NK-1) receptor antagonist fosaprepitant. The antiemetic medication with ondansetron is continued until the first postoperative day and dexamethasone is administered until the third postoperative day. Fortunately, using this combination, there has been no severe nausea monitored postoperatively in any patient undergoing HIPEC. To maximize staff safety, HIPEC is performed using the closed technique (fig. 2) as the OR personnel are less exposed to chemotherapeutics compared to the open technique [41]. The selection of this method knowingly accepts that the distribution of the heated liquid within the abdomen is not optimal. The patient is changed into a supine position. 2 inflow tubes are positioned, 1 infraastrically with a heat-sensor probe and the other in the Douglas cavity. Then 3 outflow drains are arranged below the liver, under the spleen and near the bladder – 2 of them with a probe for temperature monitoring. After checking the correct position of the tubes, the skin is closed using a monofilament resorbable suture with high tear strength. All tubes are connected to the closed extracorporeal sterile circuit. Initially, preheated saline solution is used to fill the cavity and drive out trapped air. Approximately 3–4 l of saline solution is required to achieve circulation at a flow rate of 1,500 ml/min. At temperatures ranging from 42–43°C, the chemotherapy agent (cisplatin) is added to the perfusate and circulated for 90 min. At least one experienced surgeon needs to be present to secure an even flow through all tubes during the entire procedure and ensure that there is no leakage of chemotherapeutic agent-containing fluid. An important step in reducing staff exposure is decreasing the number of team members present in the OR during
perfusion. Only the surgeon checking the flow of circulation and the seal of the provisional suture and the anesthesiologist need to remain in the OR. Other protective measures at the start of HIPEC include safety glasses for the remaining staff, double impermeable gloves and reinforced gowns. At the end of the procedure the perfusate is drained into the waste container and the abdomen is washed with approximately 3 l of sterile saline solution to dilute resident drugs. Finally, the abdominal cavity is carefully inspected; the abdominal fascia and the skin are closed properly, usually leaving 2 drains for postoperative drainage of the abdomen. All cytotoxic waste has to undergo specified disposal and the nurses are instructed to treat all body fluids as contaminated.

Postoperative Management

Postoperatively our patients were transferred to the ICU. Particular attention has to be paid to the hydration and a sufficient renal function, especially as cisplatin is a nephrotoxic agent. Furthermore, the outflow of the HIPEC drains has to be monitored, as does the correct location and functioning of any chest tubes that may have been placed intra- or postoperatively in the case of extensive diaphragm resections to avoid pleural effusion. Blood tests, including differential blood count, serum electrolytes, creatinine, liver parameters and pancreatic lipase from serum, and tests on drainage fluids should be performed on admission to the ICU and 6 and 24 h postoperatively to detect surgical complications or severe adverse effects such as anastomotic leakage, pancreatic fistula, a neutropenia or a renal failure. The early monitoring for lipase or amylase is to detect spontaneous intestinal perforations after performing HIPEC, which may occur as a consequence of intestinal lesions, heat and cytotoxic agents. If surgical complications are suspected, early CT scans should be taken. Complications induced by chemotherapy are recorded based on the National Cancer Institute Common Toxicity Criteria (CTC). Prophylactic antibiotics and primary prophylaxis of neutropenia with the application of G-CSF was not performed due to the lack of evidence-based data. On average, patients were transferred back to the gynecological ward after 4 days. Although 67% of patients were able to leave the ICU on postoperative day 2 or 3, prolonged stays could be caused by systemic inflammatory response syndrome and the need for catecholamines. Frequent observation is required on the ward until the patient is discharged.

Discussion

HIPEC is a complex and challenging procedure that demands a multidisciplinary team and specific institutional and professional requirements. The high costs of this treatment and the need for cost-benefit analyses should not be neglected. Despite the multitude of international publication on HIPEC, there is still no uniform strategy or standardized procedure for performing HIPEC. Although several techniques have been used, amongst others the open or closed methods, as yet there is no proof as to which is superior. The different methods of administrating HIPEC vary in the choice of cytostatic drugs and dosages, the timing of parietal closure (before or after HIPEC), targeted intraperitoneal temperatures, duration of HIPEC perfusion, type of perfusate and the flow rate [42]. Comparison of the heterogeneous data is also limited by the varying patient population comprising primary and recurrent as well as chemoresistant and chemosensitive ovarian cancer. Reported studies mostly comprise small populations, coming from different centers with individual selection criteria, which make it difficult to establish a standard [40, 43–46]. Most experience with this therapeutic approach exists in the treatment of mesothelioma and metastatic colorectal cancer [15]. The feasibility, however, has not only been proven, but is also clearly reflected within the guidelines of International and German Society for Visceral Surgery for the treatment of colorectal carcinoma. The AGO’s reserved assessment of any intraperitoneal therapeutic approach led into an increasing number of patients with ovarian cancer being treated mostly by general surgeons using HIPEC without established guidelines. This development in Germany does not seem to be the appropriate way of securing the best possible medical treatment of gynecological patients with advanced ovarian cancer. However, given the findings of a significant benefit in progression-free and overall survival for patients receiving intraperitoneal administration of chemotherapy, this therapeutic approach seems to be very promising [5]. In particular, the most feared and serious complications of postoperative adjuvant intraperitoneal chemotherapy, such as adhesions or catheter-associated complications, are negligible using HIPEC.

Compared to neighboring European countries and the USA, Germany has missed taking part in the scientific developments in this field. For this reason and due to the still very poor prognosis of patients with advanced ovarian cancer, we should be motivated to develop and maintain know-how in this medical field.

As a consequence of the very inhomogeneous data, at our cancer center we initiated a phase I trial investigating the maximal tolerable dose (MTD) of cisplatin in HIPEC in patients with recurrent ovarian cancer. A classic 3 + 3 design was used, enrolling 3 patients first at a dose level of 60 mg cisplatin/m² BSA, checking if no dose limiting toxicity occurred, with the next 3 patients receiving 80 mg cisplatin/m² BSA. Finally, in the last level, patients received 100 mg cisplatin/m² BSA. 12 patients in all were treated according to protocol and only 1 dose-limiting toxicity, a temporary renal insufficiency, occurred at the level of 100 mg/m² BSA, so that this level was repeated successfully with another 3 patients. The results of this study including pharmacological and pharmacokinetic data demonstrated that a dose of 100 mg cisplatin/m² was safe and feasible [23]. There was no increase in perioperative morbidity, and, in addition to HIPEC, all patients received standard therapy. The initiation of this single-center study supported us in the implementation of this therapeutic method, and the results encouraged the development of a multi-center, prospective, randomized and controlled phase III trial in which patients with advanced ovarian cancer are treated by an adjuvant and/or neoadjuvant procedure com-
bined with HIPEC. The realization of this trial protocol, presently undergoing the review process by the ‘Deutsche Krebshilfe’, depends on the participation and successful implementation of this therapeutic approach into gynecological oncology practice. Interest for introducing this treatment is high, and the conditions for establishing this procedure within the scope of a study are good. Fortunately, many centers are already applying HIPEC routinely, and several prospective randomized trials in Europe and the USA are currently examining HIPEC as a standard therapy in ovarian cancer at different points of treatment (www.clinical-trial.gov). The challenges for a randomized clinical trial looking at outcome in ovarian cancer are the requirement of many hundred patients and the collaboration among several gynecological oncology centers performing HIPEC all using the same standardized procedure. It is time for gathering and analyzing a significant set of data to prove or refute the value of HIPEC as a part of the standard therapy for advanced ovarian cancer patients.

In conclusion, the implementation of HIPEC into gynecological oncology practice can be done safely and in a standardized way. Standardization of this treatment option is the best way to reduce morbidity and mortality. Establishing this therapeutic method in expert centers for ovarian cancer requires a multidisciplinary approach. However, due to the lack of homogenous data, it is not advisable to introduce this treatment outside of clinical trials. Hopefully the opportunity to join prospective trials will be provided in the near future.

Disclosure Statement

There are no financial disclosures or conflicts of interest from any of the authors.

References


