Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Ovarian Cancer: Evaluation of Side Effects in a Single Institution Cohort

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Abstract. *Background/Aim:* Peritoneal carcinomatosis is a sign of advanced ovarian cancer. If cytoreductive surgery results in a tumor-free situation with the remaining tumor being less than 0.25 cm, Hyperthermic intraperitoneal chemotherapy (HIPEC) may further improve prognosis. *Patients and Methods:* Patients with ovarian cancer and peritoneal carcinomatosis underwent cytoreductive surgery. In 43 patients with optimal tumor debulking, HIPEC was performed. The peri- and post-operative course was observed. Adverse events were recorded after the Clavien-Dindo classification. *Results:* The median age of the patients was 56 years, the median peritoneal cancer index (PCI) was 13, and the median operation time was 356 min. There was no postoperative surgery associated death. No adverse events were recorded in 16 (37.2%) of 43 patients, no grade III or IV adverse events were reported for 33 (76.7%) patients, and no grade IV adverse events were reported for 41 (95.3%) patients. Grade III adverse events occurred in 19 (44.2%) of the 43 patients. Grade IV adverse events occurred in 3 (7.0%) of the 43 patients. *Conclusion:* In ovarian cancer, multiple surgical procedures may be necessary in order to have macroscopically eradicated tumor tissue. The combination with HIPEC, further improves survival of patients with peritoneal carcinomatosis.

In Germany, epithelial ovarian cancer is the leading cause of gynecologic cancer mortality with 5,354 deaths and 7,250 new

diseases of ovarian cancer in the year 2014. Most patients with advanced stage cancer will experience recurrence and die as a result. The five year relative survival for women diagnosed with stage FIGO III and IV epithelial ovarian cancer has changed little over the years and remains around 20-30%. Thus, more effective treatment strategies are needed (1).

In most cases of advanced cancer the peritoneum is the primary site of spread and failure, even in relapses. In view of this, it seems logical to assess local treatment strategies apart from peritonectomy. Prior studies have shown that intraperitoneal delivery of cisplatin is associated with a 20-fold higher concentration in the intraperitoneal space, compared to that measured in plasma after intravenous administration. Several randomized clinical trials have shown that postoperative intraperitoneal and intravenous (*i.p./i.v.*) chemotherapy improves survival in women with optimally resected stage III ovarian cancer compared with *i.v.* chemotherapy alone. Yet many factors have been identified as potential barriers to integration of *i.p./i.v.* chemotherapy into clinical routine. Treatment-related toxicities, adhesion barriers after surgery, dysfunction of implanted *i.p.* catheters (Tenckhoff catheters), the absence of a standard treatment regimen, patients' preference and the inconvenience of an inpatient regimen are some of the more frequently reported hinderances (2).

Hyperthermic intraperitoneal chemotherapy (HIPEC) is usually applied immediately following peritonectomy procedure with the aim of directly delivering a heated cytotoxic drug to the peritoneal surface of the abdomen. While cytoreductive surgery removes macroscopic disease, the purpose of HIPEC is to eradicate microscopic disease from the peritoneal surface. Studies have shown that hyperthermia enhances penetration of the cytotoxic agent and induces tumor cell death by multiple mechanisms. These include impairing DNA repair, inhibiting angiogenesis and inducing apoptosis. The treatment rationale is that HIPEC can penetrate and eradicate tumors up to a diameter of 2.5 cm, so

This article is freely accessible online.

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Key Words: Hyperthermic intraperitoneal intraoperative chemotherapy, HIPEC, ovarian cancer, side effects, cisplatin.

that any cancer left should be smaller than this for HIPEC to be most effective. Advantages of HIPEC compared with postoperative *i.p.* chemotherapy are that no adhesion barriers exist at the time of operation and that there is no need of a tenkoff catheter. Furthermore, the effectiveness of intraoperative intraperitoneal chemotherapy is increased by the hyperthermic application (3-8). So far, all these advantages are only theoretical.

While there is data concerning the efficacy of the method, there are hardly any reports as to the side effects of this treatment option. This was enough reason to evaluate the adverse effects of hyperthermic intraperitoneal intraoperative chemotherapy in patients with advanced or recurrent ovarian cancer.

Patients and Methods

We performed a case series analysis of patients treated with HIPEC for ovarian cancer. An interdisciplinary team of one specialized gynecologic oncologist and abdominal surgeons who performed all surgical procedures according to standard operative treatment guidelines of advanced or recurrent ovarian cancer. Forty three patients were included either with advanced ovarian cancer or with recurrent ovarian cancer between October 2014 and April 2016. The criteria for inclusion were as follows: 1) patients with histopathologically proven primary stage III ovarian, fallopian tube and primary peritoneal carcinoma, 2) patients with interval debulking surgery after neoadjuvant chemotherapy+, and 3) patients with recurrent ovarian, fallopian tube and primary peritoneal carcinoma.

HIPEC was performed at the end of the operation. All 43 HIPEC procedures were performed using a closed method. Cisplatin was used at a dose of 50 mg/m² and was diluted in 3 l of NaCl solution for peritoneal dialysis. Initially, 3 l of a heated perfusion solution was infused into the abdominal cavity at a rate of 1000-3000 ml/min through the inflow tube using the Bemont Hyperthermic pump. The intraabdominal thermometers (one positioned in the pelvis, and the second in the diaphragma area) were used to monitor the temperature inside the peritoneal cavity during the infusion, which was kept constant at 42°C. The duration of the HIPEC procedure was 60 min, after which the perfusion solution was completely drained.

In all patients the peritoneal cancer index was routinely determined using the Sugarbaker classification (9). This shows the results of a single institution prospective cohort with 43 patients who after optimal cytoreductive surgery for advanced ovarian cancer with tumor size less than 0.25 cm were treated with HIPEC (with the exception of one patient). The adverse effects of hyperthermic intraoperative chemotherapy are reported. To analyze the side effects, the Clavido-Dindo classification was used (10).

Results

Biometric data and the surgical procedures are summarized in Tables I and II. The median age of the patients was 56 years (range=32-74 years), the median peritoneal cancer index (PCI) was 13 (range=4-21), the median operation time was 356 minu (range=192-507 min).

In 40 (93.0%) of the 43 cases a CC-0 resection was reached. Of these 40 patients, 24 patients were treated by primary debulking surgery, three patients by interval debulking surgery and 13 patients received surgery for recurrences.

A CC-1 resection was performed in 7.0% of the cases (primary treatment: n=2, treatment for recurrences: n=1).

In these 43 patients, 142 peritonectomy procedures (right and left upper quadrant, paracolic right and left, pelvis, mesentrium, anterior abdominal wall, bursa omentalis) were performed. The median number per patient was 4 procedures (range=0-8 procedures). Pelvic peritonectomy was performed in 36 patients (83.7%). No peritonectomy was performed in 6 (14.0%) patients, and 25 (58.1%) patients had 4 or more than 4 peritonectomy procedures.

In total, 145 visceral resections were performed in these 43 patients. The median number per patient was 4 resections (range=0-11). Greater omentectomy was performed in 70.5% of patients, partial gastrectomy in 2.3%, splenectomy in 18.2%, cholecystectomy in 11.4% and partial pancreatectomy in 2.3%. Hysterectomy was performed in 63.6 % of patients. In 10 (23.3%) patients, more than 4 visceral resections were performed.

There were three different anastomotic procedures (ileocolic, colocolic, colorectal). The total number of anastomosis in all patients was 56 with a median of 1 per patient (range=0-3). The most common anastomosis was a colorectal anastomosis, which was performed in 36 patients (83.7%).

A total of 5 ostomies in 11.6% of patients were necessary: 4 (9.3%) were diverting ileostomies to protect a colorectal anastomosis and in one case (2.3%) a permanent colostomy had to be performed.

Thirteen patients (30.2%) received 1 to 4 units fresh frozen plasma and 8 (18.6%) patients received more than 4 units. In 9 patients (20.9%) no fresh frozen plasma (FFP) in the operating room was necessary. Only 6 (14.0%) patients received a transfusion of more than 6 units of whole blood. Nineteen (44.2%) patients did not need blood transfusions.

All patients were treated with HIPEC with 50 mg/m² cisplatin in the operating room. There was no early postoperative intraperitoneal chemotherapy added. The median time to postoperative systemic treatment with chemotherapy was 29 days (range=21-70 days). There was no postoperative death in this group of 43 patients.

No adverse events were recorded in 16 (37.2%) of the 43 patients, no grade III or IV adverse events were reported for 33 (76.7%) patients, and no grade IV adverse events were reported for 41 (95.3%) patients.

The grade III and IV adverse events are summarized in Table III. Grade III adverse events occurred in 19 (44.2%) of the 43 patients. A total of 29 grade III adverse events were reported in 19 patients. Twelve of these 29 adverse events were pleural effusions after peritonectomy at the diaphragma. Grade IV adverse events occurred in 3 (7.0%)

Table I. Patient characteristics.

Patients	n=43
Median age	56 years (range=32-74 years)
Median peritoneal cancer index (PCI)	13 (range=4-21)
Median duration of operation	356 min (range=192-507 min)

Table II. Surgical procedures.

	n=56 (from 43 patients)
Anastomosis	n=1
Partial gastric resections	n=8
Splenectomies	n=5
Cholecystectomies	n=5
Protective ileostomies	n=0
Insufficiencies of anastomoses	n=1
Leakages induced by drainages	

Table III. Adverse events grade III and IV.

Adverse events	Grade III n	Grade IV n
Total adverse events	29 at 19 pat. (44.2%)	3 at 3 pat. (7.0%)
Haematology	10	0
Leucocytopenia/thrombocytopenia	3	0
Transfusion >4 units	7	0
Renal failure	2	0
Electrolyte abnormalities	1	0
Pleural effusions	12	0
Gastrointestinal	1	0
Insufficiencies of anastomoses	0	0
Fistula	0	1
Infections	2	0
Thromboembolism	1	0
Cardiac events (reanimation)	0	1
Wound infection with operative revision	0	1

of the 43 patients. A total of 3 grade IV adverse events were reported.

Two grade IV adverse events resulted in return to the operating room. This was a fistula of the distal small bowel caused by drainage and a revision of wound infection. The remaining grade IV adverse events did not require surgical intervention.

Discussion

Ovarian cancer is a leading cause of cancer related death in women and is often only diagnosed at an advanced stage, then with diffuse peritoneal carcinomatosis. Since ovarian cancer is mainly confined to the peritoneal cavity, even after recurrence, it is an ideal target for locoregional therapy. Up until recently, most of the evidence for HIPEC in the treatment of advanced ovarian cancer was based on large retrospective series (11-13), a few small non-randomized prospective studies (14, 15) and a small randomized trial of low quality in terms to study design (16). These available studies are difficult to interpret and compare due to the heterogeneity of the study groups. A clear distinction between primary and recurrent disease, extensiveness of peritonectomy surgery, various FIGO stages and types of histology, although these aspects significantly influence the outcome. A systemic review of published trials (17) identified 9 comparative studies reporting an improvement in survival following cytoreductive surgery (CRS) and HIPEC [+/- chemotherapy (CHT)] compared with CRS alone (+/- CHT). Morbidity following CRS and HIPEC has been reported to be between 12% and 33% (17, 18). The

majority of complications are more likely due to the aggressive CRS rather than HIPEC, particularly in respect to bowel complications (anastomotic insufficiencies, bowel fistula sepsis). However, the addition of HIPEC is associated with renal impairment and haematological toxicity due to transient bone marrow suppression.

The results of the first RCT for HIPEC for primary ovarian cancer were published in 2018 (19). In this study, hyperthermic intraperitoneal chemotherapy with 100 mg/m² cisplatin was administered at 40°C over 90 min in an open technique. Sodium thiosulfate was administered by a six-hour intravenous infusion to prevent nephrotoxicity. The hazard ratio (HR) for disease recurrence or death was 0.66 (95%CI=0.50-0.87, $p=0.003$), favouring the HIPEC group. The median PFS was 14.2 months in the CRS plus HIPEC group *versus* 10.7 months in the CRS group. At 5 years, 50% of the patients in the CRS plus HIPEC group had died *versus* 62% in the CRS group (HR=0.67, 95%CI=0.48-0.94, $p=0.02$). The median OS was 45.7 months *versus* 33.9 months, showing a 11.8-month survival advantage in the CRS plus HIPEC group. There was no significant difference in grade III or IV adverse events between the two groups (27% *vs.* 25%, $p=0.76$, respectively). There was a higher rate of stoma formation in the CRS plus HIPEC group (72% *vs.* 43%, $p=0.04$). Despite this, the overall health-related quality of life outcomes did not differ between the two groups. To date this is the best evidence that a single administration of HIPEC given at the time of cytoreductive surgery for ovarian cancer may achieve significant benefits in terms of survival without excess morbidity or loss of quality of life. However, there has been a critique concerning this study, in the direction of a

possible premature analysis of overall survival, the heterogeneity of results between study centres, and the results being applicable to only a small subset of patients with ovarian cancer (20). The HIPEC arm also received an additional, high dose of cisplatin compared to the non-HIPEC arm, which in itself might explain the improved survival.

In contrast to the results of this aforementioned study, preliminary results from a smaller Korean RCT of HIPEC in 184 women with stage III and IV ovarian cancer failed to show a significant difference in five-year survival in the HIPEC arm (21). Yet it remains unclear how many women in this study had residual disease less than 2.5 mm. Also, cases of stage IV disease were included. Given the importance of achieving minimal residual disease confined to the peritoneal cavity for HIPEC to be most effective, the results of the Korean trial must be analysed more thoroughly before conclusions can be drawn about the validity of these findings. More recently, a phase III RCT of HIPEC for stage IV colorectal cancer did not show a survival benefit over systemic chemotherapy following cytoreductive surgery (22).

As yet, the type of medication used and dose of intraperitoneal chemotherapy remains unclear. In the first German prospective HIPEC ROC I trial with 12 patients suffering from recurrent ovarian cancer, Zivanovic *et al.* (23) demonstrated that increasing dosages from 50 mg/m² cisplatin to 100 mg/m² are safe. Thus, the conclusion was that 100 mg/m² cisplatin should be used in future studies. They observed one case of renal failure without the need for dialysis. The mean operation time was 463 min and the time to systemic chemotherapy was no longer than 6 weeks. In this case series the dosage of 50 mg/m² cisplatin was used, because the results of Zivanovic *et al.* (23) were not available when our case series started. Furthermore, we did not want to influence the incidence of adverse events negatively with the risk of prolonging the time to systemic chemotherapy (TTC).

When exactly postoperative systemic chemotherapy (TTC) should begin remains controversial. The main prognostic factor for survival is the radicality of debulking surgery with the aim of achieving CC-0 resection. Nevertheless, in a systemic review of 3,326 patients of the AGO-OVAR trials 3, 5, and 7 Mahner *et al.* (24) showed that a time interval to chemotherapy of more than 19 days is combined with a significant decline in prognosis, especially for those patients without macroscopic residual tumor after debulking surgery. These results stand in concordance to the results of Hofstetter *et al.* (25). They evaluated the data of 191 patients of the European multicenter OVCAD trial in which patients had a median time to chemotherapy of 28 days (range=4-158 days). They could show that patients with remaining tumor after debulking surgery had a significantly worse overall survival when starting chemotherapy later than 28 days after CRS. Feng *et al.* (26) have reported on 625 patients with

advanced ovarian cancer and a median time to chemotherapy of 15 days (range=4-62 days). They could demonstrate that a time to chemotherapy of up to 6 weeks does not negatively effect the prognosis. In our trial the median time to chemotherapy was 29 days with a range of 21 to 70 days. The patient with a TTC of 70 days that negatively influenced the total result of TTC was the patient with a fistula of the ileum caused by a drainage resulting in several operations.

As already pointed out above, the most important prognostic factor is the radicality of cytoreductive surgery (CRS) with a significantly better prognosis for patients with total tumor resection after CRS. (27-30). Hofstetter *et al.* (25) have described a R0 resection in 63.4% of the patients in their trial and Feng *et al.* of 33.4%. In 93.0% of the patients of our case series a CC-0 resection and in 7.0% a CC-1 resection was achieved. Thus, the number of patients with CC-0 resection in our case series is significantly higher than in the comparable studies of Hofstetter *et al.* (25) and Feng *et al.* (26).

In our case series adverse events of grade III following the Clavien Dindo classification (10) were observed in 19 patients (44.2%) with 29 grade III adverse events. Twelve of these 29 adverse events were pleural effusions after peritonectomy at the diaphragma. There were 3 adverse events of grade IV in our case series: one small bowel fistula caused by the drainage had to be reoperated, one successful cardiopulmonary reanimation and one wound infection with secondary operative revision. All these adverse events occurred in three patients (7.0%). There was no postoperative death.

In their trial with 142 patients with colorectal carcinomas and CRS with HIPEC Yonemura *et al.* (31) have reported one postoperative death due to pulmonary thromboembolism. Grade III adverse events were described in 7.7% and grade IV adverse events in 9.9% of cases, mainly concerning anastomotic insufficiencies and fistulas of the bowel. Pleural effusions were not reported. Kuijpers *et al.* (32) have reported grade III adverse events in 34% of the 960 patients with colorectal tumors treated by CRS and HIPEC. Three % of the patients died after surgery. Passot *et al.* (33), with 216 patients with peritoneal carcinomatosis of different origin (35% ovarian cancer) treated with CRS and HIPEC have reported a 42% incidence of grade III and IV adverse events.

The fact that we had a high rate of CC-0 resection and different peritoneal and anastomotic procedures in our case series, makes it difficult to compare our data to the above mentioned literature concerning morbidity and mortality.

Because of our heterogenous cohort no survival data can be presented. The main aim was to evaluate the feasibility and morbidity of HIPEC combined with cytoreductive surgery followed by standard platin and taxan based chemotherapy. CRS and HIPEC with 50 mg/m² cisplatin in ovarian cancer is a feasible treatment option. The time to chemotherapy (TTC) in our setting was not markedly prolonged. The main complications are surgically caused and not the result of the

HIPEC procedure. The low incidence of grade III and IV adverse events without any perioperative mortality in our case series suggests that HIPEC with 50 mg/m² cisplatin after CRS in ovarian cancer does not cause intolerable adverse events or is of disadvantage for patients with ovarian cancer. The very low leakage rate with only one case of a fistula of the small bowel shows the immense importance of the experience of the surgical team and the complication rate with respect to insufficiencies of anastomoses.

In summary, the data presented is not a proof of the efficacy for the approach with HIPEC in the treatment of ovarian cancer which is an experimental one at the moment. It has to be emphasized that HIPEC is currently only indicated by National Comprehensive Cancer Network® (NCCN) guidelines for administration in the interval debulking setting, in patients with stage III disease. There is currently no indication in the recurrent setting or after primary debulking surgery.

Conclusively, cytoreductive surgery with the use of HIPEC should not be performed outside these guidelines unless there are study conditions in experienced centers. Prospective trials are needed.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Prof. Dr. Clayton Kraft: Translation; Prof. Dr. Walther Kuhn: Corrections in form and content; Wolfgang Zinn: Analysis and interpretation of data; Prof. Dr. Michael Friedrich: Surgeon; Laura Kolnsberg: Medical care during hospital stay.

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Received January 8, 2020

Revised January 23, 2020

Accepted January 27, 2020