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Chapter

HIPEC for Ovarian Cancer: A Controversial Discussion

Michael Friedrich, Dominique Friedrich, Clayton Kraft, Walther Kuhn and Christoph Rogmans

Abstract

Peritoneal carcinomatosis is a sign of advanced disease of ovarian cancer. The prognosis of ovarian cancer is significantly improved after cytoreductive surgery with complete tumor debulking followed by platin based chemotherapy. If cytoreductive surgery results in a tumor free situation with remaining tumor less than 0.25 cm, HIPEC may further improve prognosis. Materials and methods: The results of the Krefeld study are presented and the literature is reviewed according to overall survival and progression free survival with or without HIPEC. In the Krefeld study, patients with ovarian cancer and peritoneal carcinomatosis underwent cytoreductive surgery. In patients with optimal tumor debulking, HIPEC was performed. The peri- and postoperative course was observed. Adverse events were recorded after the Clavien-Dindo classification. Results: 43 patients were treated with cytoreductive surgery and HIPEC. In all patients an optimal cytoreductive situation with remaining tumor less than 0.25 cm was achieved. HIPEC was performed with a cisplatin solution (50 mg/m2) at 41°C. 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 minutes (range: 192–507 minutes). The median time to postoperative systemic treatment with chemotherapy was 29 days (range 21–70). There was no postoperative surgically 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 occured in 19 (44.2%) of the 43 patients; a total of 29 grade III adverse events were reported in these 19 patients. Grade IV adverse events occured in 3 (7.0%) of the 43 patients; a total of 3 grade IV adverse events were reported. Two of them 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. Conclusion: In ovarian cancer multiple surgical procedures may be necessary in order to have macroscopically eradicated tumor tissue. Combined with HIPEC, this seems to have positive effects on the survival of patients with peritoneal carcinomatosis. Since we have no marked additional adverse events caused by HIPEC in our case series, HIPEC seems to be an additional treatment option of peritoneal carcinomatosis in ovarian cancer. This statement is strengthened by the literature review in that metaanalysis show significant improved OAS and PFS.

Keywords: Hyperthermic intraperitoneal intraoperative chemotherapy, HIPEC, ovarian cancer

1. Introduction

Most patients with advanced ovarian cancer will suffer from recurrence, because the five year overall survival for stage FIGO III and IV epithelial ovarian cancer is still very low with 20–30%. Thus, gynecologic oncologists are looking for better treatment strategies [1].

In most patients with advanced ovarian cancer the spread to the peritoneum is the primary site of failure. Thus, it seems reasonable to assess additional local treatment strategies apart from maximal tumor debulking. According to prior studies the intraperitoneal application of cisplatin is assiciated with a 20-fold higher concentration in the intraperitoneal space compared to that measured in plasma after intravenous administration. Furthermore it was shown that the combination of postoperative intraperitoneal and intravenous (ip/iv) chemotherapy improves survival in women with optimally resected stage III ovarian cancer compared with iv chemotherapy alone. There are many aspects like 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 inpatientregimen that prevent the integration of ip/Iv chemotherapy into clinical routine [2].

2. Review and discussion

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 macroscopic disease is removed by cytoreductive surgery, microscopic disease from the peritoneal surface should be eradicated by HIPEC. There are studies showing that hyperthermia enhances penetration of the cytotoxic agent and induces tumor cell death by multiple mechanisms including impaired DNA repair, inhibition of angiogenesis and induction of apoptosis. The rationale of applicatio of HIPEC is that HIPEC eradicates tumors up to a diameter of 2.5 cm. Advantages of HIPEC in comparison to postoperative ip chemotherapy are the missing adhesion barriers at the time of operation. Furthermore, the effectiveness of intraoperative intraperitoneal chemotherapy is increased by the hyperthermic application [3–9].

In our own case series analysis [10] of 43 patients treated with HIPEC (cisplatin 50 mg/m2 for 60 minutes at 42°C) for advanced or recurrent ovarian cancer there was no postoperative death. Adverse events of grade III following the Clavien Dindo classification [11] were observed in 44.2% of the patients, which suggests that HIPEC with cisplatin 50 mg/m2 after CRS in ovarian cancer is a feasable treatment option. Additionally, the time to chemotherapy (TTC) was not markedly prolonged in our setting. The main complications are caused by surgery and not by HIPEC procedure. The very low rate of insufficiences of anastomoses with only one case of a fistula of the small bowel shows the immense importance of the experience of the surgical team.

Yonemura et al. [12] described in their study with CRS and HIPEC for colorectal carcinomas one postoperative death caused by pulmonary thromboembolism. Grade IV adverse events were observed in 9.9% of cases mainly due to insufficiences of anastomosis. Grade III adverse events were reported by Kuijpers et al. [13] in 34% of the 960 patients in a simliar trial with a mortality rate of 3%, while Passot et al. [14], found an incidence of grade III and IV adverse events in 42% of 216 patients (CRS and HIPEC) with peritoneal carcinomatosis (35% ovarian cancer).

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 [15–34]. Peritoneal carcinomatosis represents the advanced stage in the evolution of

EOC, which has been considered as the main cause of recurrence [23, 35, 36]. Since ovarian cancer is mainly confined to the peritoneal cavity, even after recurrence, it is an ideal target for locoregional therapy. IP chemotherapy is not a standard treatment option because of concerns of excessive toxicity [37–39]. Nevertheless IP chemotherapy is associated with improved survival of advanced EOC [6–8]. HIPEC and postoperative IP chemotherapy are differing distinctly from eachother, because HIPEC is a single treatment of intraoperative chemotherapy at the time of cytoreductive surgery. Some critical aspects of ip chemotherapy may be eliminated by this fact [21]. So far, most of the evidence for HIPEC in the treatment of advanced ovarian cancer was based on large retrospective series [15–17], a few small non-randomized prospective studies [18, 19] and a small randomized trial of low quality in regard to study design [20]. These available studies are difficult to interpret and compare due to the heterogenicity of the study groups. A clear distinction between primary and recurrent disease, extensiveness of peritonectomy surgery, various FIGO stages and types of histology is not made, although these aspects in themselves significantly influence the outcome. A systemic review of published trials [21] identified 9 comparative studies reporting an improvement in survival following CRS and HIPEC (+/− CHT) compared with CRS alone (+/− CHT). Morbidity following CRS and HIPEC was reported to be between 12% and 33% [21, 22]. The majority of complications are more likely to be due to the aggressive CRS rather than HIPEC, particularly in respect to bowel complications (anastomotic insufficiences, bowel fistula sepsis). On the other hand 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 [23]. In this study, hyperthermic intraperitoneal chemotherapy with cisplatin 100 mg/m2 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 three or four 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 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 [24]. 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.

This study provided the evidence of survival benefit by HIPEC in patients with intervall debulking surgery in advanced EOC. One hast o keep in mind that the survival of the group without HIPEC was shorter than that in the Gynecologic Oncology Group–172 study perhaps because of the different inclusion criteria (intervall debuling surgery versus primary debulking surgery) [40].

In contrast to the results of Van Driehl et al., a smaller Korean RCT on HIPEC with 184 women, including only patients with stage 3 and 4 disease, did not

demonstrate a significant advantage in terms of five-year survival in the HIPEC arm [25]. It is not described in how many patients the remaining tumor mass was less than 2.5 mm. In addition, women with extraperitoneal metastatic ovarian cancer were also included in the study. However, it is important for HIPEC therapy to have minimal residual tumor. Therefore, the Korean study would need to be reevaluated from these perspectives to gain valdie insights. For stage IV colorectal carcinoma, a recently published phase III RCT HIPEC trial failed to demonstrate a survival benefit over systemic chemotherapy after cytoreductive surgery [26].

Which drugs and in what dosage should be used for intraperitoneal chemotherapy is still unclear. Zivanovic et al. [27] showed in the first prospectively designed German HIPEC-ROC-I study of 12 patients with recurrence of ovarian cancer that a dose increase from 50 mg/m2 cisplatin to 100 mg/m2 is safe. Although one patient in the study experienced renal failure not requiring dialysis, a dose of 100 mg/m2 cisplatin should be used in future studies. The mean operative time was 463 minutes. In all cases, systemic chemotherapy was started within 6 weeks. We used the dosage of 50 mg/m2 cisplatin in our study, because at the beginning of the study the results of Zivanovic et al. [27] had not been published.

Nevertheless, it is not clear at which point it is appropriate to start postoperative systemic chemotherapy (TTC). The most important prognostic factor regarding OS is achieving surgical R0 resection. At the same time, Mahner et al. [28] demonstrated in a systemic review of 3,326 patients from three AGO-OVAR trials [3, 5, 7] that delayed initiation of therapy of more than 19 days in R0 resected patients was associated with significantly decreased overall survival. In contrast, patients with macroscopic residual tumor did not benefit from an earlier start of chemotherapy. Hofstetter et al. [29] support these findings. An analysis of the European multicenter OVCAD trial in which the median start of chemotherapy was 28 days (range 4 to 158 days) demonstrated that patients with macroscopic R1 resection had significantly worse overall survival, when chemotherapy was started after 28 days or later. In contrast, Feng et al. [30] demonstrated in 625 patients with advanced ovarian cancer that an interval of up to 6 weeks between cytoreductive surgery and start of chemotherapy did not negatively affect overall survival. The median TTC in our study was 29 days (range 21–70 days). The late start of therapy with a TTC of 70 days was due to a fistula at the ileum that required multiple surgeries.

As already mentioned, surgical R0 resection is the most important prognostic factor associated with significantly improved overall survival. When evaluating the studies described above, this must be taken into account. In Hofstetter et al. [29], 63.4% of the patients had R0 resection, whereas in Feng et al. [30], this was 33.4%. In our study, R0 resection was achieved in 93% of cases, and only 7% of cases had R1 resection.

Wu et al. [41] demonstrate in their metaanalysis, that HIPEC can significantly improve the OS and PFS of EOC. But so far HIPEC is not accepted as a standard treatment in clinical routine [21] because of the heterogeneity of the inclusion criteria and the study methods.

Wu et al. [41] demonstrate in their metaanalysis, that HIPEC significantly improves the OS and PFS of EOC. But so far HIPEC is not accepted as a standard treatment in clinical routine [21] because of the heterogeneity of the inclusion criteria and the study methods. Subgroup analysis, which considered study design, adjusted for heterogeneity. Nevertheless, there are only two RCTs on HIPEC in ovarian cancer. The different lengths of follow-up made it necessary to perform further analyses regarding to OS and PFS.

Even in this analysis there is the suggestion that HIPEC could significantly improve survival. Consistent with previous studies [23, 42] Wu et al. [41] also found that the administration of HIPEC is safe, with limited and less morbidity and

mortality compared with no HIPEC group in the majority of included studies. In primary EOC patients, Wu et al. demonstrated that HIPEC improved OS, PFS and each year survival rate. In addition, these results are consistent with previous meta-analysis of HIPEC [21] suggesting that the incorporation of HIPEC may result in better prognosis of primary EOC [40]. Most previous evidence of a beneficial effect from HIPEC in primary EOC has been limited to single-group trials or retrospective cohorts [43–48]. Until recently, van Driel et al. [23] reported the first RCT about primary EOC and HIPEC with the evidence of HIPEC's survival benefit in advanced EOC after NAC.

Lei et al. [49] perfomed a cohort study from January 2010 to May 2017 at 5 high-volume institutions in China to compare survival outcomes between PCS with HIPEC vs. PCS alone for patients with stage III epithelial ovarian cancer. A total of 584 patients with stage III primary epithelial ovarian cancer were treated with either PCS alone or PCS with HIPEC. The median follow-up period was 42.2 (33.3–51.0) months.

In addition, a distinction was made how the resection grade of tumor mass affected the 3-year overall survival rate and median survival time. In patients with R0 resection with additional HIPEC, median survival was 53.9 months (95% CI, 46.6–63.7) and 3-year overall survival was 65.9% (95% CI, 60.1%–71.2%). Patients with residual tumor who underwent HIPEC therapy had a median survival of 29.2 months (95% CI, 22.3–45.5) and a 3-year overall survival rate of 44.3% (95% CI, 34.6%–53.4%). In patients with complete tumor mass reduction who received PCS only, median survival was 42.3 months (95% CI, 31.1–59.3), and 3-year overall survival was 55.4% (95% CI, 44.7%–64.8%). Incomplete tumor mass resection without HIPEC, exhibits the worst outcome with a median survival of 19.9 months (95% CI, 11.6–39.1) and a 3-year overall survival rate of 36.7% (95% CI, 23.4%–50.1%). This leads to the conclusion that PCS with HIPEC results in significantly better overall survival, especially with R0 resection of tumor mass.

In contrast, several studies in the past lead to opposing results. This could be due to heterogeneous study designs, different treatment regimens, and different inclusion criteria of patients. Mendivil et al. [50] performed a comparative study in primary advanced EOC, highlighting survival rates of patients with and without HIPEC treatment. Here, a significant PFS advantage was evident in the HIPEC group, although overall survival was not prolonged. The reason could be the different recruitment period of the cohorts. The control group was recruited much earlier (2008–2014) and thus had a longer median follow-up time in contrast to the HIPEC group, which was collected in 2012–2015. This could be the reason for the similar median OS of both groups. Wu et al. [45] also failed to show a significant PFS benefit in their study regarding HIPEC therapy. Interestingly, the rate of complete tumor reduction was only 14.58% in the control group and 8.33% in the HIPEC group. As shown above, this could have a strong impact on the data analysis.

Additional trials are still needed to determine the optimal time for HIPEC administration and whether HIPEC is also effective after primary cytoreductive surgery in aprospective randomized trial.

For recurrent ovarian cancer, Wu et al. showed that HIPEC therapy significantly increased OS and PFS. These results are in accordance with similar meta-analysis of Huo et al. on HIPEC [21]. Cascales-Campos et al. confirmed the results regarding significant differences in 2-, 4-, and 5-year PFS with and without HIPEC therapy [42]. It is well known that the standard treatment of relapsed EOC is systemic chemotherapy. The median OS is less than 30 months [21]. Nevertheless, there is evidence that even in relapsed EOS, prognosis can be improved by CRS, provided that the tumor can be completely resected [51, 52]. Bristow et al. showed that patients who underwent CRS had OS ranging from 41 to 60 months. The PFI was

30.3 months [51, 52]. Again, the complete tumor mass reduction was crucial for median overall survival (R0 45.2 vs. R1 19.7, HR¼3.71, p < 0.001) [53]. These data demonstrates that overall survival in relapsed EOS can be significantly increased by CRS. Implementation of CRS in the therapy of relapsed EOC would improve overall survival. This may be a reason, which could have led to insignificant difference for 1- and 2-year PFS for therapy with and without HIPEC. Baiocchi et al. [54] showed that overall survival cannot be improved by combining CRS and HIPEC in relapsed platinum-sensitive EOC. Further studies are needed for recurrent EOC, especially considering tumor resectability.

But this result might be based on a selection bias with regard to the different extent of disease or surgery status. It has to be taken under consideration, if the result might be based on a selection bias with regard to the different extent of disease or surgery status. Spiliotis et al. [20] demonstrated in their randomized trial of 120 relapsed EOC patients that the combination of CRS and HIPEC was superior to CRS only. Surprisingly, overall survival rates were the same in the HIPEC cohorts regardless of the presence or absence of platinum resistance. This was not the case in the CRS group. The reason for this could be sensitization of tumor cells by hyperthermia. It is conceivable that molecular mechanisms, such as heat shock proteins or epigenetic changes, could be triggered to sensitize the tumor cells [55, 56]. Again, complete tumor reduction is shown to prolong median overall survival. A limitation could be the randomization process and primary endpoints of the study are not clearly defined [23, 57]. In conclusion, further RCS on relapsed EOC need to be performed as the study situation is very heterogeneous regarding PFS, median follow-up and first-line postoperative treatment [19].

There are some limitations existing in the meta-analysis by Wu et al. First, the inclusion criteria and HIPEC drug regimens for EOC are varying with regard to the extent of disease status and CRS, to the standardization of IPEC protocols. Second, no standard quantitative measurement of the morbidity related to HIPEC was established. Third, the potential publication bias of included studies was unavoidable due to insufficient RCTs data so far.

It is expected that additional RCS will be performed in the future to elucidate the value of HIPEC in primary and recurrent EOC. In previous studies, the common thread was the performance of HIPEC following CRS. Platinum and/or paclitaxel were usually chosen as therapeutic agents. Only one study evaluated the combination of cisplatin and doxirubicin.

3. Conclusion

Taken together, Wu et al. support with their meta-analysis that HIPEC therapy has a positive impact, both in primary and recurrent EOC on patients' OS and PFS. Nevertheless, no improvement in 1- and 2-year PFS was achieved in recurrent EOC. Therefore, especially for relapsed disease, it is essential to design clearly structured studies that support the value of HIPEC in the treatment of EOC.

Conflict of interest

The authors declare no conflicts of interest.

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