Neoadjuvant, adjuvant and long-term intravenous/intraperitoneal chemotherapy, hyperthermic intraperitoneal chemotherapy, early postoperative intraperitoneal chemotherapy for ovarian cancer

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Abstract

Ovarian cancer is commonly diagnosed after dissemination and is accompanied by a poorer overall prognosis. Treatment incorporates a multimodal approach, utilizing various combinations of surgery and chemotherapy. Ultimately, better screening tests are needed for ovarian cancer to help reduce the burden of advanced-stage disease. For those women with advanced-stage tumors, newer therapeutic strategies may help prolong survival and increase the chance for cure. The aim of this study is to review current trends in the treatment of women diagnosed with advanced-stage epithelial ovarian cancer. Therapeutic practices are analysed concerning neoadjuvant chemotherapy (NACT), intraperitoneal chemotherapy (IPC), adjuvant chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC), and early postoperative intraperitoneal chemotherapy (EPIC) and long-term intravenous/intraperitoneal (IV/IP) chemotherapy in ovarian cancer.

Introduction

The aim of this study is to review current trends in the treatment of women diagnosed with advanced-stage epithelial ovarian cancer.

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Key words: Gynecologic cancer; ovarian cancer; hyperthermic intraperitoneal chemotherapy; early postoperative intraperitoneal chemotherapy; cytoreductive surgery; neoadjuvant chemotherapy; clinical trials.

Conference presentation: paper presented at the *10th International Congress on Peritoneal Surface Malignancies*, Washington, DC, November 17-19, 2016.

Received for publication: 28 February 2017.
Revision received: 3 July 2017
Accepted for publication: 11 July 2017.

Journal of Peritoneum (and other serosal surfaces) 2017; 2:59
doi:10.4081/joper.2017.59

Neoadjuvant chemotherapy in epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is a major cause of cancer-related mortality in women. Although cytoreduction is the best treatment for the management of advanced ovarian cancer, there are some factors that make it difficult to achieve complete cytoreduction in certain patients. Patients with poor performance status and unresectable disease are candidates for NACT. However, there are no uniformly validated selection criteria for immediate referral to NACT.[1]

The group of Aletti *et al*.,[2] identified a subgroup of patients in whom the benefits from aggressive debulking do not appear to outweigh the risks. Those very high-risk group could be identified by the following three criteria: high tumor dissemination or stage IV, poor performance status (ASA ≥3), poor nutritional status (preoperative albumin levels <3.0g/dL) or age ≥75 years. In this group, the resulting morbidity seems too high to justify aggressive surgical effort. The median overall survival was only 17 months. In this study, NACT approach is proposed to be the best option for this small group of patients.

Women who undergo NACT typically receive primary platinum and taxane based chemotherapy, followed by interval cytoreduction and additional cytotoxic therapy postoperatively. Institutional series have noted that perioperative morbidity is often reduced in women who undergo NACT, compared to those treated with a strategy of primary cytoreductive surgery (CRS).[3,4]

A meta-analysis, including 835 patients, showed that NACT treatment is associated with inferior overall survival compared to initial surgery. Each 10% increase in cytoreduction is associated with an increase in 1.9 months of median survival. In the same study within the rate of 3-6 cycles, each incremental chemotherapy cycle was associated with a decrease in 40.1 months in median survival so the surgery ought to be done as early in the treatment programme as possible.[1]

Administration of NACT treatment is not at present in the literature as primary cytoreduction. Much of the evidence describing

the outcomes of NACT is based on retrospective institutional reports that have compared the outcomes of primary cytoreduction to a strategy of NACT.[3-10] Many of these studies have noted that NACT is associated with less perioperative morbidity and a higher rate of optimal cytoreduction than primary cytoreduction.

A meta-analysis of 21 studies by Kang *et al*., found that patients who received NACT were less likely to undergo a sub-optimal cytoreduction (pooled odds ratio 0.50; 95% CI, 0.29-0.86).[6]

Another study by Hou *et al*., compared 109 patients who underwent primary surgery to 63 women treated with NACT. A higher rate of optimal cytoreduction in those treated with NACT was noted (95% *vs* 71%). Furthermore, aggressive surgery was required in only 5% of those women who received NACT, compared to 25% in the primary surgery group. The median overall survival in the NACT group was 46 months, similar to the 47 months noted in the primary surgery patients.[4]

An institutional series study by Everett *et al*., identified 200 patients with advanced stage EOC and included 98 patients who had initial chemotherapy and 102 who underwent surgery. Surgical morbidity was similar between the two groups, however optimal cytoreduction was more often achieved in patients who underwent NACT (86% *vs* 54%, P<0.001). In the survival analysis, optimal cytoreduction was the only independent factor of improved survival. Timing of cytoreduction either as primary surgery or after NACT, was not associated with survival.[3]

The only randomized controlled trial of primary surgery *versus* NACT was undertaken by the European Organization for Research and Treatment of Cancer (EORTC) and reported in 2010. The study randomized 670 patients with stage IIIC-IV EOC to primary cytoreduction followed by platinum-based chemotherapy or neoajuvant platinum-based chemotherapy. Optimal cytoreduction to a largest tumor diameter of <1 cm was achieved in 41.6% of patients who underwent primary debulking compared to 80.6% of those who received NACT. Perioperative morbidity rate was 0.7% in the NACT group compared to 2.5% in the primary surgery group of patients. Median overall survival was comparable between the two arms, 29 months in the primary surgery group and 30 months in the NACT group of patients. The investigators concluded that NACT was not inferior to primary surgery.[10]

For NACT, a platinum/taxane doublet is recommended. However, alternate regimens containing a platinum agent, maybe selected based on individual patient factors. Since the publication of GOG 111, GOG 158 and AGO-OVAR3,[11-13] the standard of care first-line treatment of advanced EOC, has been six cycles of carboplatin and paclitaxel. In the EORTC trial, 83% of patients received treatment with a combination of carboplatin and paclitaxel delivered every 3 weeks. However, only 76% of the CHORUS study[14] participants received both carboplatin and paclitaxel. Nearly 24% were treated with single-agent carboplatin. Alternate regimens were used rarely in both trials: 6.3% of participants in EORTC trial and 1% in CHORUS received another chemotherapy combination.

Randomized controlled trials (RCT's) tested surgery following three or four cycles of chemotherapy in women who had a response to NACT or stable disease. Interval cytoreductive surgery should be performed after ≤4 cycles of NACT for women with a response to chemotherapy or stable disease. RCT's have not address whether the timing of interval cytoreductive surgery or the number of chemotherapy cycles after interval cytoreductive surgery affect the safety or efficacy of treatment. In both the EORTC and CHORUS studies, patients received three cycles of NACT before interval cytoreductive surgery (ICS) and three cycles thereafter. In the JCOGO602 study,[15] ICS followed 4 cycles of carboplatin and paclitaxel, but survival data from this trial is expected in 2017.

A retrospective study was conducted in three main oncology centers in the east of France by Akladios *et al*., reviewing patients who underwent NACT for stage EOC between 1998-2012.[16] Of the 204 patients included, 75 (36.8%) underwent ≤4 NACT cycles and 129 (63.2%) ≥5 NACT cycles. Characteristic data were similar in the two groups. Five year overall survival (OS) was 35.0 and 25.8% respectively. This difference though was non-significant [HR=1.06 (0.70-1.59), P=0.79]. The investigators found no differences in progression free survival (PFS) or morbidity between the two groups. They concluded that the number of NACT cycles does not seem to play a role in the OS of the patients with advanced EOC.

Rates of cytoreduction to <1cm (and no visible disease) are higher among patients treated with NACT, compared with primary cytoreductive surgery, but have less prognostic significance[17] Despite data describing the potential benefits of NACT for advanced EOC, the topic remains controversial.[18-20]

The relatively poor survival and low overall rate of optimal cytoreduction in the EORTC trial have raised the concern that the results of this data are not applicable to US patients who have access to gynecologic oncologists skilled in aggressive CRS.[20] In a single institution study patients who met the eligibility criteria for the EORTC trial and who underwent primary cytoreductive surgery were identified. In this report the median OS was 50 months, superior to the overall survival of both the NACT and the primary surgery arms of the EORTC study.[21]

Many observational studies comparing outcomes of primary surgery *versus* NACT for EOC are limited by strong selection bias.[3-9,22,23] Patients with advanced age, higher grade and stage and more medical comorbidities are often been treated with NACT. In addition, patient characteristics such as volume and distribution of tumor, often influence decision making. RCT's examining NACT vs primary surgery in EOC are challenging. One reason is that among gynecologic oncologists there is often a strong bias towards one treatment or the other, limiting referral to trials. Another reason, is that enrollment of patients into clinical trials where they are randomized to either surgical approach or NACT is often problematic. Lastly, ovarian cancer patients are treated over the course of many years.[24]

Great interest has been observed lately in using observation data to explore primary treatment for EOC. Such studies are limited by both selection bias and the influence of multiple measured and unmeasured confounders that influence both treatment selection and outcomes.[25]

In order to investigate how to improve the survival of patients with advanced EOC, a retrospective study in West China reviewed 399 patients with stage IIIC or IV EOC from 2005-2010. 114 and 225 patients underwent NACT followed by IDS and PDS, respectively.[26] No difference was observed in progression-free survival (PFS) or overall survival (OS) between NACT group and PDS group (PFS: 11 *vs* 10 months, P=0.629; OS: 25 *vs* 25 months, P=0.992). The investigators concluded that NACT followed by IDS provides equal survival compared to PDS. To date, improved survival has been demonstrated in large phase III studies, proposing IP/IV chemotherapy,[27,34] dose-dense paclitaxel[35] and the addition of bevacizumab for patients with inoperable or suboptimally cytoreduced disease.[36] At some institutions, clinicians have replaced the 3-week administration of paclitaxel with the "dose-dense" weekly approach, because of the superior survival demonstrated in JGOG 3016.[35]

Adjuvant chemotherapy in epithelial ovarian cancer

In the last three decades there have been significant improvement in the chemotherapeutic options for patients with EOC.[27-30]

In the 1970s and 1980s treatment often included doxorubicin and cyclophosphamide. In the 1980s, the platinum analogous showed efficacy and are still considered the most active agents for EOC. Since then, series of studies examined alternative strategies to administer these agents, and tested how novel biologic agents can be used for the treatment of ovarian cancer. Despite the advances, the choice of the best therapy for individual patients often remains elusive. Increased efficacy of chemotherapy is often accompanied by increased toxicity. Major challenges for oncologists include how to balance efficacy, toxicity and quality of life in decision making. The standard of care for the adjuvant therapy of advanced stage ovarian cancer changed rapidly in the mid-1990s with the presentation of the taxanes. The GOG protocol 111, randomized 386 patients with suboptimal cytoreduction (>1 cm residual tumor) to 6 cycles of chemotherapy, with either cyclophospamide and cisplatin or cisplatin and paclitaxel. Overall response rate was 60% in the cisplatin/cyclophoshamide group compared to 73% in the cisplatin/paclitaxel group. With a median follow up of 37 months, median progression free survival was 13 months in the first group, compared to 18 months in the second arm (P<0.0001). Median OS was 24 *vs* 38 months, respectively.[30]

Another trial, OV10, compared cisplatin/cyclophosphamide to cisplatin/paclitaxel.[31] Analysis of 680 patients revealed a response rate as well as progression-free survival and overall survival to be superior in the paclitaxel treated patients. The GOG protocol 158, randomized 792 patients to treatment either with cisplatin/paclitaxel or carboplatin/paclitaxel and found that carboplatin/paclitaxel combination was less toxic, easier to administer, and not inferior to the cisplatin-containing doublet. Since then, carboplatin and paclitaxel remain the most frequently used regimen for ovarian cancer.[32] In subsequent studies, modifications of the carboplatin-paclitaxel backbone for ovarian cancer added additional cytotoxic agents to upfront therapy. GOG protocol 182, randomized patients to carboplatin and paclitaxel with some combination of gemcitabine, liposomal doxorubicin or topotecan, given either as triplets or sequential doublets. Analysis revealed no difference in survival for any of the combinations.[33-36]

At many institutions, patients do not receive IP/IV chemotherapy after NACT+ICS, and at present data is limited, except of two studies: i) a phase II Southwest Oncology Group Study, that studied the use of IP/IV chemotherapy after NACT+ICS in stage III/IV ovarian cancer patients, of whom optimal cytoreduction was thought to be unlikely on imaging. Only 26 patients of the 58 received NACT, ICS and postoperative IP/IV chemotherapy. In this group the median progression-free and overall survival were 29 and 34 months, respectively;[37] ii) a multinational randomized phase II study, PETROC/OV21 compared IP/IV carboplatin and paclitaxel versous continued treatment with IV carboplatin and paclitaxel, among women treated with NACT and optimal ICS.[38] In an interim analysis in abstract form, IP/IV chemotherapy was found to be both feasible and safe to use after NACT.[39] A comparison of the rates of progression-free survival at 9 months showed 42.2% of women randomized to receive IV chemotherapy had progressive disease compared with 23.3% of those who received IP/IV chemotherapy.

Increasing interest has been noted in the molecularly targeted agents, with the greatest interest focusing on bevacizumab, a humanized anti-vascular endothelial growth factor. GOG protocol 218,[29] randomized 1873 women with incompletely resected stage III and IV ovarian cancer, to chemotherapy with carboplatin and paclitaxel to three arms: placebo, bevacizumab for 6 cycles, or bevacizumab during chemoptherapy as a consolidation therapy for a total of 22 cycles. The median progression-free survival (PFS) was 10.3 months in the control group, 11.2 in the bevacizumab during chemotherapy arm, and 14.1 in the prolonged bevacizumab arm. PFS was statistically significant longer in the prolonged bevacizumab arm compared to the control arm. Median overall survival was 39.3, 38.7 and 39.7 months respectively.[29]

A second study with bevacizumab reported similarly improved PFS in favor of the use of bevacizumab. The benefits were greatest in patients at highest risk for recurrence.[28]

Intraperitoneal chemotherapy in epithelial ovarian cancer

Intraperitoneal chemotherapy (IP) delivery of chemotherapy has a proposed pharmacokinetic advantage over the systematic therapy, because of the presence of the peritoneal-plasma barrier that maintains a high concentration gradient of cytotoxic drug between the peritoneal cavity and the plasma compartment. The molecular weight and the charge of the drug determine the absorption of intraperitoneal chemotherapy (IPC) to the systemic circulation. Highly charged hydrophilic large molecules are more effectively sequestered in the peritoneal cavity, resulting in a higher area-under-the curve ratio at IP than observed in the systemic chemotherapy. The most commonly used agents in ovarian cancer, cisplatin and paclitaxel have peritoneal-to-plasma concentration ratios of 20:1 and 1000:1, respectively.[40,41]

Given that ovarian cancer predominantly spreads within the peritoneal cavity, there is a strong rationale for this method of delivery. Studies have demonstrated that IP delivery of chemotherapy results in higher cellular concentration of a number of agents. The feasibility of IP chemotherapy has been shown in a number of phase II and phase III trials.[27,42]

A large randomized controlled trial reported by the Southwest Oncology Group (SWOG), randomized 654 patients with optimally cytoreduced ovarian cancer to either IV cyclophospamide + cisplatin or an experimental regimen of IV cyclophosphamide with IP cisplatin. The IP arm was associated with an 8 month improvement in overall survival (49 vs 41 months).[42]

The GOG 172 protocol examined 429 women, optimally cytoreducted for ovarian cancer and randomized them either to IV cisplatin and paclitaxel or an experimental arm of IV paclitaxel on day1, IP cisplatin on day 2, and IP paclitaxel on day 8 (IP arm). IP chemotherapy was associated with an improvement in both, progression-free (24 vs 18 months) and overall (66 vs 50 months) survival. Accompanied greater toxicity was though noted to the improved survival of the patients. It is worth mentioning though that while quality of life for the IP arm of the study was worse, there was no difference in quality of life between the 2 arms, 1 year after treatment.[27]

In 2016, a study conducted by Boisen *et al*., noted that second-line intraperitoneal platinum-based therapy, leads to an increase in second-line progression-free survival for EOC.[43] This was a retrospective analysis of women who received combination of platinum-based IV/IP chemotherapy for recurrent EOC, between 2005 and 2011. The first and second treatment-free interval (TFI) were defined as the time from the end of previous platinum-based therapy, to the start of the next therapy. 25 women received IV/IP chemotherapy for their first EOC recurrence after IV chemotherapy. In 10 patients (40%) the investigators observed a longer TFI after IV/IP chemotherapy than after primary IV chemotherapy. For these 10 patients , the median TFI for primary response was 22 months (range 15-28), whereas median TFI after IV/IP chemotherapy for recurrent disease was 37 months (range 12-61). The investigators concluded that for EOC patients with limited peritoneal

recurrence, 40% of patients had a second-line IP-platinum TFI that exceeded their front-line IV-platinum TFI, compared to published data. These data support the use of IV/IP chemotherapy as a treatment for recurrence.[43]

In 2006, the National Cancer Institute (NCI) announced: *On the basis of the results of randomized phase III clinical trials, a combination of IV and IP administration of chemotherapy conveys a significant survival benefit among women with optimally debulked ovarian cancer, compared to IV administration alone*.[44] Despite the NCI endorsement, the IP approach for EOC remains the subject of scientific debate, and has not been widely adopted into the routine clinical practice. Concerns about toxicity, dosing, patients tolerability and catheter-related complications (port infection or occlusion), have continued to impede its acceptance in the medical community.[45]

Fujiwara *et al*. retrospectively analyzed the recurrence and survival of 174 EOC patients who were treated with first line IP carboplatin therapy.[46] 22 patients were treated with carboplatin alone, 116 with carboplatin + cyclophosphamide, and 27 patients with carboplatin + paclitaxel, as a chemotherapy regimen. The median number of chemotherapy cycles was 6 and the median number of IP cycles was 5 (IP therapy well tolerated). The response in 54 patients with measurable disease was 66.4%. The 5-year survival was 94.4% for stage I and 87.9% for stage II disease. The median survival for optimal and suboptimal stage III-IV patients was 51 months and 34 months respectively. Of note, the median survival of patients with stage III-IV disease was 51 months with carboplatin doses of 400 mg/m^2 or more, but it was only 25 months with carboplatin doses lower than 400 mg/m^2.

Currently, there are three ongoing large-scale prospective randomized trials, examining the efficacy of carboplatin-based IP therapy.

- The GOG252 trial aims to improve tolerability of IP therapy and compare PFS and OS to an IV arm. The study has three arms: i) IV carboplatin+IV dose-dense paclitaxel; ii) IP carboplatin+IV dose-dense paclitaxel; and iii) IV paclitaxel+IP cisplatin+IP paclitaxel. All three arms, also receive bevacizumab 15 mg/kg followed by an additional 18-month maintenance.
- The JGOG3019 phase III trial is evaluating IV carboplatin *vs* IP carboplatin with both arms receiving dose-dense weekly IV paclitaxel.
- Finally, a unique trial is the OV-21/GCIG study, led by the Canadian National Cancer Institute. Patients with stage III EOC receive NACT and the responders undergo IDS. If residual disease after IDS is <1 cm, the patient is randomized to one of three treatment arms: i) control arm with combination of IV paclitaxel followed by IV carboplatin on day 1 and then IV paclitaxel on day 8; ii) arm 2 is the same as the control, however, carboplatin will be given by the IP route; and iii) arm 3 is the modified GOG172 arm (same as GOG252 trial but bevacizumab is not given).

One of the first IP doublet studies was conducted by Muggia *et al*.[47] It enrolled 18 patients in a phase I study of IP carboplatin and IP etoposide. At a median follow-up of 4 years, 8 patients (out of 18) are alive and four had no evidence of disease 1 to 4 years after treatment onset. A subsequent study by Muggia *et al*. enrolled 16 patients with similar peritoneal small-volume recurrence of EOC and was a phase I/II study of IP platinums (cisplatin or/and carboplatin) and floxuridine (FUDR), a metabolite of 5-fluorouracil (5-FU).[48] Overall, the combination of FUDR and both platinums were particularly well tolerated. The median time to progression was 15 months, with the survival being in excess of 26 months with 8 of 11 patients alive at minimum follow-up of 32 months (range 32-34).

Another study by Muggia *et al*. extended observations of above doses of IP cisplatin +FUDR: 14 patients with stage II ovarian cancer were enrolled to receive this regimen as consolidation after induction with carboplatin and paclitaxel and a negative second-look surgical assessment.[49] The mean number of cycles administered was 3.2 and the median time to recurrencewas 19.4 months.

Chambers *et al*. investigated the feasibility and pharmacokinetics of IP cyclosporine, followed by a phase II dose-escalation of the combination of IP cyclosporine and carboplatin in refractory EOC patients.[50] The pharmacologic advantage demonstrated in this study is interesting in the support of future studies using IP cyclosporine for the modulation of platinum resistance.

Hyperthermic intraperitoneal chemotherapy, early postoperative intraperitoneal chemotherapy, sequential intraperitoneal chemotherapy and salvage chemotherapy for epithelial ovarian cancer

The addition of hyperthermia to IPC is rationalized by the observed increase in response of the tumor to the cytotoxic drugs. This phenomenon is explained by the direct antitumor effect of heat, in addition to hyperthermia-induced selective cytotoxicity of malignant cells.[51] It was noticed that the cytotoxic effects of some chemotherapeutic agents (doxorubicin, cisplatin, mitomycin C, melphalan, docetaxel, irinotecan, and gemcitabine) and augmented by hyperthermia.[52] IPC is given by different schedules and techniques including HIPEC, EPIC, sequential intraperitoneal chemotherapy (SIPC), and bidirectional IPC. HIPEC is the only technique performed utilizing hyperthermia and administered in the operating room on the same day of surgery, while EPIC and SIPC are both normothermic regimens administered for more than one day. EPIC is usually given for 4-6 days after surgery, while SIPC is a repetitive treatment administration over 6 months. Bidirectional IPC is a new modality in which IPC and IV chemotherapies are administered concurrently.[53,54] To maintain the efficacy and safety of HIPEC the drug's heat stability should be confirmed. Almost all drugs are stable under moderate hyperthermic conditions. Sugarbaker *et al.*[55] reported stability data for some chemotherapeutic medications after dilution for IP use at room temperature.

Two case-control studies reported recently the advantage of cytoreductive surgery (CRS) and HIPEC in ovarian cancer. Cascales-Campos *et al.*[56] studied 87 patients, 52 of whom were treated with HIPEC (paclitaxel) and 35 were in the control group. The result showed that the 1 year disease-free survival was 81% *vs* 66,0% and 3 year disease-free survival was 63.0% *vs* 18.0% (P<0.05). Multivariate analysis revealed that HIPEC was an independent prognostic factor for OS. Another study from Greece conducted a double-blind prospective phase III clinical trial on CRS+HIPEC in patients with recurrent ovarian cancer. All 120 patients had stage IIIC/IV ovarian cancer and experienced disease recurrence after initial surgical treatment and first-line systemic chemotherapy. They were randomized in two groups. Group A comprised 60 patients treated with CRS+ HIPEC and then systemic chemotherapy. Group B comprised 60 patients treated with CRS only and systemic chemotherapy. The mean survival was 26.7 months in Group A *vs* 13.4 months in Group B (P<0.01), and the 3 year survival was 75.0% for Group A vs 18% for Group B (P<0.01). In the HIPEC group the median survival did not differ between patients with platinum resistant disease and platinum sensitive disease (26.6 months *vs* 26.8 months).[57]

In 2006, a study by Silber *et al*. evaluated ovarian cancer survival with the SEER database for the patients treated with chemotherapy by a medical oncologist or gynecologic oncologist. Although both groups of physicians are trained to provide medical treatment to ovarian cancer patients, substantial differences in the patterns of care emerged based on the patient's provider. During the first 5 years of care for ovarian cancer, patients treated by medical oncologists received more weeks of chemotherapy than patients treated by gynecologic oncologists (patient mean 16.5 *vs* 12.1 weeks respectively, P<0.0023). This increase in chemotherapy administration translated into increased adverse events. Gynecologic oncology patients had fewer weeks that included chemotherapy associated adverse events than medical oncology patients (patient mean 8.9 *vs* 16.2 weeks respectively, P<0.0001). No survival advantage was achieved for patients receiving chemotherapy administered in the long-term setting by the medical oncologist.[58]

An ongoing phase III RCT (randomized controlled trial), named *CHORINE* by Ansaloni *et al*. compares two-years disease-free survival of CRS (cytoreductive surgery) and HIPEC [HIPEC, CDDP (cisplatin) + paclitaxel] *versus* CRS alone in stage IIIc unresectable epithelial tubal/ovarian cancer with partial or complete response after 3 cycles of 1st line chemotherapy (CBDCA+paclitaxel). Results are pending.[59]

CHIPOR is another ongoing phase III RCT by Classe *et al*. *CHIPOR* hypothesis is that the adjunction of platinum HIPEC in first relapsed EOC is able to improve the median OS (overall survival) by 12 months. The patients included in the study receive - before surgery - a second line chemotherapy, platinum-based regimen with either carboplatin-paclitaxel or carboplatin-caelyx. At the end of six courses IV chemotherapy, if the patient is a responder and if complete CRS is possible, the patient will be operated 5 to 6 weeks after the second line chemotherapy cycle. During surgery the patient is randomized (if complete CRS is done or not) to either: i) treatment A: maximal CRS without HIPEC; or ii) treatment B: maximal CRS with HIPEC. Results are pending.[60]

Hipecova is an ongoing phase III RCT, by Campos *et al*., evaluating the efficacy of HIPEC with paclitaxel in advanced ovarian cancer. There are two arms: i) the HIPEC arm: CRS+HIPEC with paclitaxel (175 mg/m^2) X 60 min at 42-43°C followed by postoperative systemic IV chemotherapy with carboplatin + paclitaxel X 6 cycles; ii) the no HIPEC arm: CRS followed by postoperative systemic IV chemotherapy with carboplatin + paclitaxel. Results are pending.[61]

A phase III, multicenter prospective RCT by Cui *et al*. examines the safety and efficacy of HIPEC as NACT and postoperative chemotherapy after IDS in the treatment of advanced stage EOC. Patients in arm A will have: i) HIPEC with paclitaxel (100 mg/m^2), paclitaxel (75 mg/m^2) + cisplatin (75 mg/m^2) intraperitoneally in succession; ii) 2 cycles of NACT: paclitaxel 175 mg/m^2 IV > 3 h + carboplatin IV > 1 h every 3 weeks; iii) IDS; iv) HIPEC with paclitaxel 100 mg/m^2, paclitaxel (75 mg/m^2) + cisplatin (75 mg/m^2) intraperitoneally in succession; v) 2 cycles of ACT (adjuvant chemotherapy): paclitaxel 175 mg/m^2 IV >3 h + carboplatin IV > 1 h every 3 weeks. Patients in arm B will have: i) 3 cycles of NACT: paclitaxel 175 mg/m^2 IV > 3 h + carboplatin IV > 1 h every 3 weeks; ii) IDS; iii) 3 cycles of ACT: paclitaxel 175 mg/m^2 IV > 3 h + carboplatin IV > 1 h every 3 weeks. This study has not opened yet for recruitment.[62]

Another phase III RCT study by van Driel *et al*. evaluates the safety and efficacyof the addition of HIPEC to secondary debulking surgery in stage III ovarian cancer. The study is not recruiting anymore. Results are pending.[63]

A systematic review and meta-analysis by Huo *et al*. included a total of 9 comparative studies and 28 studies examining HIPEC+CRS for primary and/or recurrent EOC. Meta-analysis of the comparative studies showed HIPEC + CRS + chemotherapy had significantly better 1-year survival compared with CRS + chemotherapy alone (OR: 3.76, 95% CI 1.81-7.82). The benefit of HIPEC and CRS continued for 2-, 3-, 4-, 5-, and 8- year survival compared to CRS alone (OR: 2.76, 95% CI 1.71-4.26; OR: 5.4, 95% CI 3.24-7.85; OR: 3.51, 95% CI 2.00-6.17; OR: 3.46, 95% CI 2.19-5.48; OR: 2.42, 95% CI 1.38-4.24 respectively). Morbidity and mortality rates were similar. Pooled analysis of all studies showed that among patients with primary EOC the median 1-, 3-, and 5- year overall survival rates are 46.1 months, 88.2%, 62.7%, and 51%. For recurrent EOC the median 1-, 3-, and 5-year overall survival rates are 34.9 months, 88.6%, 64.8% and 46.3%. A stepwise positive correlation between completeness of CRS and survival was found. The authors concluded that the addition of HIPEC to CRS and Chemotherapy improves overall survival rates for both primary and recurrent EOC.[64]

The purpose of a retrospective Italian multicenter observational study of 511 cases, by Di Giorgio *et al*., was to help with the process of selecting patients with advanced ovarian cancer, to undergo CRS + HIPEC by analyzing the outcome data at distinct clinical time points, reflecting the natural history of the disease: primary debulking surgery, interval debulking surgery after partial response, after no response and after a pathologic complete response to NAC, first occurrence with a PFI of 12 months or 12 months in patients who underwent further chemotherapy, before CRS +HIPEC, and patients who underwent two or more CRS procedures and chemotherapy lines before CRS + HIPEC. Multivariate analysis showed that besides peritoneal spread (PCI) and Completeness of Cytoreduction (CC score) another equally significant independent prognostic factor influencing outcome is the time when patients undergo CRS + HIPEC. The 511 enrolled patients underwent 3.373 procedures; 72.6% achieved complete CRS with an overall major morbidity of 17.45. At a median follow-up of 53.8 months overall survival was 54.2 months (95% CI 44-58.4) and PFS was 16.6 months (95%, CI 14.7-19.1).[65]

Conclusions

The field of gynecologic oncology is faced with a number of challenges including how to incorporate new drugs and procedures into practice, how to balance therapeutic efficacy and toxicity of treatment, how to individualize therapy to particular patients and how to contain the rapidly rising costs associated with oncologic care. Ovarian cancer is commonly diagnosed after dissemination and is accompanied by a poorer overall prognosis. Treatment incorporates a multimodal approach, utilizing various combinations of surgery and chemotherapy.

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