Update on Intraperitoneal Chemotherapy for the Treatment of Epithelial Ovarian Cancer

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OVERVIEW

Surgical treatment and chemotherapy administration in women with epithelial ovarian cancer is more controversial today than at any point in the last 3 decades. The use of chemotherapy administered intraperitoneally has been particularly contentious. Three large randomized phase III studies, multiple meta-analyses, and now real-world data have demonstrated substantial outcome benefit for the use of chemotherapy administered intraperitoneally versus intravenously for first-line postoperative treatment of optimally debulked advanced ovarian cancer. Unfortunately, for each of these randomized studies, there was scope to either criticize the design or otherwise refute adoption of this route of administration. As a result, the uptake has been variable in North America, although in Europe it has been practically nonexistent. Reasons for this include unquestionable additional toxicity, more inconvenience, and extra cost. However, 10-year follow up of these studies demonstrates unprecedented survival in the intraperitoneal arm (median survival 110 months in patients with completely debulked stage III), raising the possibility that by combining maximal debulking surgery with postoperative intraperitoneal chemotherapy it may be possible to bring about a step change in the outcomes for these patients. In this review, we discuss the rationale for administering chemotherapy intraperitoneally, the merits of the main randomized clinical trials, the evidence regarding optimal regimes, issues of toxicity, port considerations, and reasons for lack of universal adoption. We also explore potential clinical and biologic factors that may be useful for patient selection in the future.

We have witnessed improvements in epithelial ovarian cancer survival over the last 3 decades without seeing significant improvements in disease-specific mortality rates (Fig. 1). Epithelial ovarian cancer remains the leading cause of death from gynecologic malignancy in North America with the majority of women presenting with stage III or IV disease.[1,2] Advances in genetic testing, counseling, and prevention with risk-reducing salpingo-oophorectomy (and salpingectomy) have the potential to produce further modest decreases in ovarian cancer mortality in the future.[3] However, we currently do not have a reliable population screening test for epithelial ovarian cancer, and, given the often nonspecific symptoms with which epithelial ovarian cancer presents, it is likely the majority of patients will continue to present with late-stage disease. Therefore, optimizing treatment is critical if we are to improve outcome. Retrospective analyses suggest that overall survival (OS) is associated with younger age, good performance status, lower stage of disease, and lower comorbidity scores.[4,5] Although histologic subtype and tumor grade previously were regarded as simply prognostic, it has now become clear that they represent pathologic markers of what are essentially discrete disease entities. These differ in terms of their tissue of origin, stage of presentation, driver molecular mutations, sensitivity to chemotherapy, and prognosis (Fig. 2). Ultimately, it is very likely that these histologic subtypes will require different treatment strategies.[6]

In clinical practice, only a few risk factors remain that can be modified based on the decisions of patients and their physicians. The surgical decision making and chemotherapy administration choices, particularly for women with stage III or IV epithelial ovarian cancer, can potentially affect survival. Informed selection of the best treatment (including clinical trial options) for any individual patient is most likely to be achieved with enthusiastically committed multidisciplinary teams working in high-volume institutions.[7,8] Discussions around chemotherapy administered intraperitoneally for individual patients require this type of environment to allow the patient to make an informed choice about care.

This article summarizes the history and role of chemotherapy administered intraperitoneally in epithelial ovarian cancer, focuses on the practical choices that patients and

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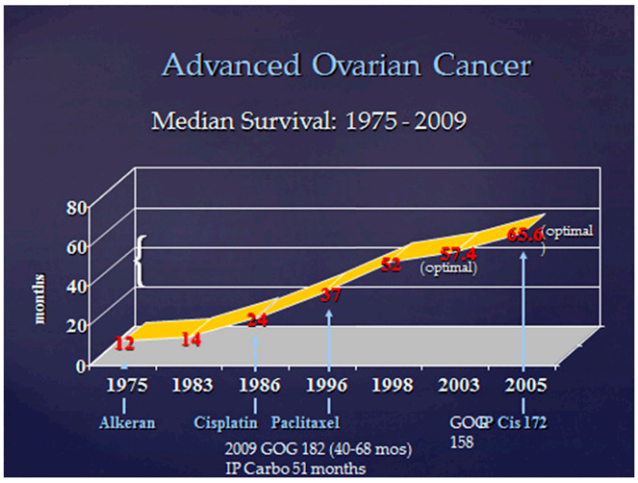
FIGURE 1. Increase in Overall Survival Over Time for Women Diagnosed With Ovarian Cancer



clinicians face (with an emphasis on emerging data), and stresses the importance of building skilled multidisciplinary teams for treating women undergoing intraperitoneal treatment. Finally, we explore how emerging data on epithelial ovarian cancer biology may be able to guide the future of intraperitoneal therapy in this disease.

RATIONALE FOR INTRAPERITONEAL CHEMOTHERAPY

The peritoneal cavity is the principle site of spread and recurrence in women with epithelial ovarian cancer. Administration of chemotherapy intraperitoneally is a means of increasing the dose intensity delivered to the tumor and minimizes systemic toxicity, therefore, it is an attractive therapeutic approach.[9] Advantages of intraperitoneal administration include high intraperitoneal concentration of the drug, as well as a longer half-life of the drug in the peritoneal cavity, compared with that observed with administration intravenously alone. For cisplatin, historically, the most extensively studied agent administered by the intraperitoneal route in epithelial ovarian cancer translates into a 10- to 20-fold greater exposure over that which is achievable with the intravenously administrated route.[10-12] Furthermore, preclinical studies suggested that cisplatin is capable of penetrating small volume tumors (1–3 mm). Hence, the hypothesis arose that the maximum benefit from administration of the drug intraperitoneally was likely to be demonstrated in patients with microscopic or low-volume macroscopic disease.[13] However, our understanding of why the intraperitoneal chemotherapy route is more effective may be oversimplified, and it has been challenged. Measurement of drug in peritoneal fluid probably does not represent actual tumor drug penetration in patients.[14] There may be added barriers in tumor implants, notably disordered capillary architecture, fibrosis, and adhesions. Furthermore, dose intensification of platinum administered intravenously has failed to show a benefit in multiple randomized studies.[15,16] However, these dose intensification studies did not select neither patients with high-grade serous ovarian cancer nor the subgroups with disease that we know to be most sensitive to platinum (those exhibiting homologous recombination deficiency, discussed below). As such, the impact in the dose-dense arms of these studies (which were twice the density of the control arm at most) in any patients with disease sensitive to this approach would be diluted out by the majority of patients whose tumor biology would make them unlikely to benefit from this approach. Although the intraperitoneal studies were similarly unselected for immunohistologic or molecular subtype, the local dose intensification in the intraperitoneal arm is potentially an order of magnitude higher than in the intravenously administrated arm. Under these circumstances, it may be possible that the signal would be evident even without preselection on the basis of histology or biology.

Other factors such as drug recirculation following peritoneal absorption may play a role in efficacy. Despite the fact that chemotherapy administered intraperitoneally has been studied for decades, we are still not fully aware of the key biologic factors that determine its success.[15,16] Moving forward, a greater understanding of how tumor biology and the immune and micro-environments are affected by treatment administered intraperitoneally may help us understand how this treatment can best be deployed and combined with the newer generation of targeted agents.

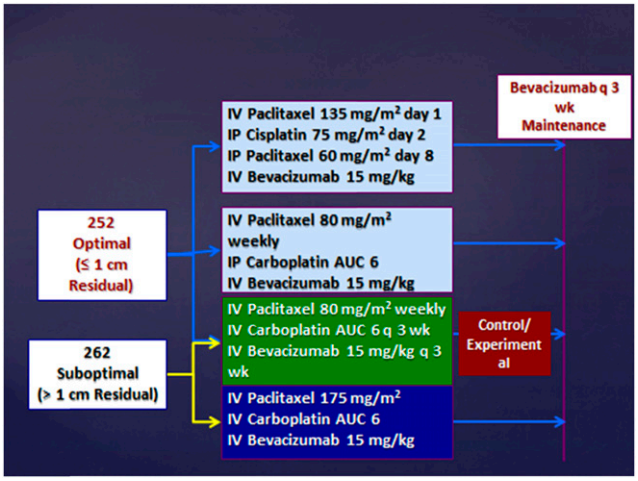
KEY POINTS

- **Patients with epithelial ovarian cancer should be treated by high-volume multidisciplinary teams.**
- **Randomized phase III trial, meta-analysis, and real-world data support the benefit of chemotherapy administered intraperitoneally in the treatment of select groups of women with epithelial ovarian cancer following up-front optimal cytoreductive surgery.**
- **The optimal intraperitoneal/intravenous chemotherapy regimen has yet to be defined, and emerging data from the randomized studies GOG 252, OV21/PETROC, and JGOG iPocc will help clarify whether cisplatin administered intraperitoneally can be replaced by carboplatin administered intraperitoneally.**
- **Discussion of chemotherapy administered intraperitoneally to treat women diagnosed with ovarian cancer is essential.**
- **Understanding the biology underlying the success of chemotherapy administered intraperitoneally is a priority; initial data suggest exploration of tumors deficient in DNA repair are of particular interest.**

INTRAPERITONEAL CHEMOTHERAPY TRIALS IN WOMEN WITH EPITHELIAL OVARIAN CANCER

Intraperitoneal chemotherapy is not a recent concept in the treatment of epithelial ovarian cancer; it was originally used

FIGURE 2. Schema for GOG 252



in the 1950s to control ascites. Interest in chemotherapy administered intraperitoneally as a strategy for reducing the risk of disease recurrence and prolonging survival emerged approximately 30 years ago. This resulted in a number of randomized phase III studies that demonstrated an improvement in survival for the combination of delivery of chemotherapy intraperitoneally and intravenously over chemotherapy administrated intravenously alone for select patients following primary cytoreductive surgery (Table 1).[17-23] GOG 172, a randomized phase III study of cisplatin administered intraperitoneally combined with both delivery of paclitaxel intraperitoneally and intravenously, published in 2006, demonstrated a 16-month improvement in median OS over intravenous administration of the same drugs alone.[18] This prompted the National Cancer Institute (NCI) to issue a rare clinical announcement regarding the clinical utility of cisplatin-based chemotherapy administered intraperitoneally in the treatment of patients with small volume (< 1 cm), advanced-stage (stage III) epithelial ovarian cancer following an attempt at maximal cytoreductive surgery. On average, intraperitoneal/intravenous chemotherapy was associated with a 21.6% decrease in risk of death (hazard ratio (HR) 0.78; 95% CI, 0.69–0.89, the original clinical announcement can be viewed at ctep.cancer.gov).

An update published in 2015 with a median follow-up of 10.7 years showed that women who underwent intraperitoneal/intravenous chemotherapy in GOG 172 continued to derive benefit with a median survival of 61.8 months (95% CI, 55.5–69.5 months) compared with 51.4 months (95% CI, 46–58.2 months) for chemotherapy administered intravenously alone.[24] The recent Cochrane Review, restricted to newly diagnosed patients receiving treatment after primary cytoreductive surgery, accepted data from eight randomized studies on 2,026 women and

TABLE 1. Summary of Randomized Clinical Trials of Intraperitoneal Chemotherapy for Up-Front Primary Cytoreductive Surgery

Study/Reference	Control Regimen	Experimental Regimen	Eligible Patients	No. of Patients
Kirmani et al[20]	Cisplatin 100 mg/m² IV cyclophosphamide 600 mg/m²	Cisplatin 200 mg/m² IP; etoposide 350 mg/m² IP	Stage IIC-IV	62
	Every 3 weeks x 6	Every 4 weeks x 6		
SWOG 8501/ GOG 104[17]	Cisplatin 100 mg/m² IV; cyclophosphamide 600 mg/m² IV	Cisplatin 100 mg/m² IP; cyclophosphamide 600 mg/m² IV	Stage III, ≤ 2 cm residual	546
	Every 3 weeks x 6	Every 3 weeks x 6		
Polyzos et al[22]	Carboplatin 350 mg/m² IV; cyclophosphamide 600 mg/m² IV	Carboplatin 350 mg/m² IP; cyclophosphamide 600 mg/ m² IV	Stage III	90
	Every 3 weeks x 6	Every 3 weeks x 6		
GONO[19]	Cisplatin 50 mg/m² IV; cyclophosphamide 600 mg/m² IV; epidoxorubicin 60 mg/m² IV	Cisplatin 50 mg/m² IP; cyclophosphamide 600 mg/ m² IV; epidoxorubicin 60 mg/m² IV	Stage II-IV, < 2 cm residual	113
	Every 4 weeks x 6	Every 4 weeks x 6		
GOG 114/ SWOG 9227[21]	Cisplatin 75 mg/m² IV; paclitaxel 135 mg/m² (24-hr) IV	Carboplatin (AUC 9) IV every 28 days x 2; cisplatin 100 mg/m² IP; paclitaxel 135 mg/m² (24-hr) IV	Stage III, ≤ 1 cm residual	462
	Every 3 weeks x 6	Every 3 weeks x 6		
Yen et al[23]	Cisplatin 50 mg/m² IV; cyclophosphamide 50 mg/m² IV; epidoroxorubin/ doxorubicin 50 mg/m² IV	Cisplatin 100 mg/m² IP; cyclophosphamide 500 mg/m² IV; epidoxorubicin/ doxorubicin 50 mg/m² IV	Stage III, ≤ 1 cm residual	118
	Every 3 weeks x 6	Every 3 weeks x 6		
GOG 172[18]	Cisplatin 75 mg/m² IV; paclitaxel 135 mg/m² (24-hr) IV	Paclitaxel 135 mg/m² (24-hr) IV; cisplatin 100 mg/m² IP; paclitaxel 60 mg/m² IP on day 8	Stage III, ≤ 1 cm residual	415
	Every 3 weeks x 6	Every 3 weeks x 6		

Abbreviations: IP, intraperitoneally; IV, intravenously.

concluded that women experienced increased survival if they received intraperitoneal/intravenous chemotherapy (HR 0.81; 95% CI, 0.70–0.9) and that intraperitoneal/intravenous chemotherapy also prolonged the disease-free interval (five studies, 1,311 women; HR 0.78; 95% CI, 0.7–0.86),[25] thus potentially affecting quality of life going forward.

Wright et al recently reported data on the real-world uptake of intraperitoneal/intravenous chemotherapy in a prospective cohort of 823 women with stage III optimally cytoreduced epithelial ovarian cancer treated in six National Comprehensive Cancer Network (NCCN) institutions.[8] Despite the trial-based evidence and although adoption of intraperitoneal/intravenous chemotherapy increased between 2007 and 2008, it plateaued with fewer than 50% of eligible patients receiving intraperitoneal/intravenous treatment. They also observed marked variation in uptake between institutions from 4% to 67%, suggesting underutilization of this effective treatment approach in this subgroup of women.

WHY HAS INTRAPERITONEAL/INTRAVENOUS CHEMOTHERAPY NOT BEEN UNIVERSALLY ADOPTED?

Despite a proven survival benefit, clearly intraperitoneal/intravenous chemotherapy has not been universally adopted for the treatment of epithelial ovarian cancer. The reasons behind this are numerous. The publication of each positive intraperitoneal/intravenous randomized study has been met with considerable debate over the interpretation of the trial data.[26] Arguments around the validity of the conclusions drawn from GOG 172 have included statistical analysis queries (intention-to-treat analysis, number of patients lost to follow-up), and questions over second-line treatment and scheduling effects.[26] The most relevant criticism of the pivotal intraperitoneal studies is the inequality of dose intensity between the treatment arms in both GOG114[21] and GOG172[18] (Table 1). Given the fact that paclitaxel administered intravenously weekly has been shown to be superior to paclitaxel administered intravenously tri-weekly in one large randomized phase III study,[27] it could be argued that the administration of an additional dose of paclitaxel on day 8 in the Armstrong study was solely responsible for the benefit demonstrated. However, a second randomized phase III study of weekly versus triweekly paclitaxel administered intravenously did not show superiority.[28] In addition, the Alberts' (GOG104) study was a clean comparison of the same doses of cisplatin administered intravenously or intraperitoneally, which demonstrated substantial progression-free and OS advantages,[17] but it was overlooked in many areas of the world because paclitaxel came to prominence and the comparator arm in GOG104 was regarded as outdated. It does, however, serve as a useful proof of principle regarding the advantages that can be attributed purely to the route of administration. In addition, when the two studies with unequal dose intensities between the arms (GOG 114 and GOG 172) were excluded from the analysis of a Cochrane systematic review in 2011, the survival benefit remained in favor of the intraperitoneal route of administration.[25] In the real-world analysis by Wright et al, 43% of patients received modified intraperitoneal/intravenous regimens over time (i.e., regimens differing from trial-specified protocols). Despite these modifications, women receiving intraperitoneal/intravenous chemotherapy continued to derive benefit over those who only received treatment intravenously (3-year OS 81% vs. 71%; HR 0.68; 95% CI, 0.47–0.99).[8]

Undoubtedly, delivery of intraperitoneal/intravenous chemotherapy requires increased resources in terms of both space and time to deliver compared with therapy administrated intravenously. Because of placement of catheters and regional delivery of drug, intraperitoneal/intravenous chemotherapy is potentially associated with greater toxicity, including catheter-related complications, gastrointestinal toxicity, pain, and infection. These have been reported across trials and supported in meta-analyses.[25,29] However, real-world reports suggest many of these potential issues can be overcome with time and development of expertise.[30,31] Furthermore, randomized data and the NCI alert support the use of cisplatin administered intraperitoneally.[17-21,23] Cisplatin is known to be more toxic than the standard of care carboplatin, which is administered intravenously for epithelial ovarian cancer.[32] To date, we do not have randomized trial data to determine whether carboplatin administered intraperitoneally is equivalent to cisplatin administered intraperitoneally in terms of its impact on survival. However, preclinical and some clinical data suggest that it might be equivalent in efficacy and less toxic than cisplatin administered intraperitoneally.[33] Results from GOG 252 (NCT00951496) and OV21/PETROC (NCT00993655) are awaited. These trials include direct comparison of regimens, including cisplatin and carboplatin administered intraperitoneally.

As yet, we have not arrived at the optimal intraperitoneal/intravenous chemotherapy regimen, which balances efficacy with toxicity and quality of life. Finally, effective and safe delivery of intraperitoneal/intravenous chemotherapy requires the multidisciplinary expertise of a skilled team, which simply may not be available in smaller-volume centers. Therefore, consideration for referral and management in high-volume centers is appropriate. Even with all the concerns that exist, it is clear that women who are appropriate for intraperitoneal/intravenous chemotherapy should be at least offered this as an option, and clinicians should be considering how best to make it available to them.[31]

SURGICAL CONSIDERATIONS FOR INTRAPERITONEAL CHEMOTHERAPY

The goal of ovarian cancer surgery whenever it is performed is no gross residual disease or R0, as defined by Chi and Bristow.[7,34] This has been shown to result in improved progression-free survival (PFS) and OS. Intraoperative

treatment decisions that have been demonstrated to influence patient survival and maximize surgical effort must include a willingness to perform diaphragm resection, splenectomy, bowel resections, and thorough peritoneal and retroperitoneal resections of tumor. This requires experience and potentially a team of surgeons.[35] Although an R0 resection improves OS, it remains somewhat unclear whether microscopic versus visible disease has an impact on intraperitoneal chemotherapy effectiveness, as the allowable residual volume at the end of surgery differed in the randomized trials ($<$ 2 or $<$ 1 cm). Many have made the assumption that patients with microscopic disease would derive the greatest benefit from intraperitoneal/intravenous chemotherapy. However, in a subgroup analysis of the GOG172 patient population, the 64% of women in GOG172 who had macroscopic (gross) residual disease less than or equal to 1 cm (which was the upper limit allowed by study eligibility) had a significant improvement in OS (HR 0.75; 95% CI, 0.62–0.92).[24] Further exploration of the effect on larger-volume residual disease should emerge from GOG-0252 and the Japanese iPocc trial (NCT01506856), both of which enrolled a proportion of patients with larger-volume residual disease.

Landrum looked into the effects of lymphadenectomy and nodal metastasis on the benefit of administering chemotherapy intraperitoneally using data from both GOG 114 and GOG 172. In these studies, despite undergoing cytoreductive surgery to less than 1 cm, only 59% of women had lymph nodes sampled or excised. Of the 254 women who had lymph node evaluation, intraperitoneal benefit in terms of PFS and OS was independent of nodal status. This suggests that chemotherapy administered intraperitoneally may be equally effective for patients with both intraperitoneal and retroperitoneal disease. Interestingly, the patients without lymphadenectomy did worse than patients with metastatic tumor removed from their lymph nodes, although the decision not to perform the lymphadenectomy may have been secondary to some poor prognostic factor perceived by the surgeon. An important long-term quality of life finding by Landrum was a decrease in recurrence in the abdominal cavity after intraperitoneal chemotherapy. Thus intraperitoneal/intravenous treatment may spare patients from suffering from ascites and an inability to eat when they recur.[4]

A key and controversial area around surgical decision making in epithelial ovarian cancer is the choice of neoadjuvant chemotherapy followed by a definitive cytoreductive surgical attempt versus primary cytoreductive surgery. Initially, neoadjuvant chemotherapy was considered only for those women who were medically unfit for aggressive surgery or for women with a high tumor burden (especially those with stage IV disease).[36,37] In recent years, the use of neoadjuvant chemotherapy has gained in popularity. This followed the publication of two studies: the European Organization for Research and Treatment of Cancer Gynecologic Cancer Group (EORTC GCG) 55971[38] and the CHORUS study,[39] which demonstrated equivalence in outcome with some reduction in morbidity for patients receiving neoadjuvant treatment. Neoadjuvant chemotherapy is usually platinum-based and administered intravenously; there is no role for intraperitoneal/intravenous therapy in the preoperative patient. A recent study by Rosen et al[40] showed that the long-term survival for patients undergoing primary cytoreduction was far superior to those receiving neoadjuvant chemotherapy and delayed primary surgery (9% vs. 41%, $p < .0001$). Although selection bias may account for some of this difference, the percentage of long-term survivors is strikingly low in neoadjuvant chemotherapy studies.[41] Patients undergoing optimal cytoreductive surgery following administration of neoadjuvant chemotherapy were not included in the previous intraperitoneal/intravenous randomized trials. Theoretically, they may derive a similar level of benefit to women undergoing up-front cytoreductive surgery from intraperitoneal/intravenous chemotherapy delivery. The combination of intraperitoneal/intravenous chemotherapy following neoadjuvant chemotherapy and optimal cytoreductive surgery is being studied in the Gynecologic Cancer Intergroup study OV21/PETROC. Women who had initial (clinical/imaging) stage IIB-IV (intravenously based on the presence of pleural effusion alone) epithelial ovarian cancer and who had received three or four cycles of platinum-based neoadjuvant chemotherapy before definitive optimal cytoreductive surgery ($\leq$ 1 cm residual disease) were eligible for this trial. Women were enrolled either intra- or postoperatively. This study has now closed and the primary analysis is expected shortly.

INTRAPERITONEAL PORT PLACEMENT

Essential to the delivery of chemotherapy administered intraperitoneally is the placement of an intraperitoneal port. Consideration of port placement should occur at the time of surgery when the port can be placed under direct visualization by the surgeon. This is the most time-efficient approach and prevents delays in the initiation of chemotherapy postoperatively. Patients should be treated as soon as they have resumed a normal diet and bowel function and are ambulatory at home, which should occur within 21 days of the primary surgery. Patients electing to receive intraperitoneal chemotherapy who do not already have peritoneal catheters can have devices implanted by interventional radiologists or surgeons familiar with laparoscopic techniques using the right upper quadrant entry techniques. Minilaparotomy in the right lower quadrant is also generally successful if resection of the terminal ileum or right colon did not occur. Careful review of the cytoreduction operative report can improve outcomes with intraperitoneal port placement to avoid complications.[42,43]

The preferred location for port placement is the right lower costal grill on the midclavicular line, below the location where the breast or the bra may be uncomfortable in a standing position. This site allows for posterior rigid support that facilitates access. Ports also are installed over the left side or right lower quadrant for convenience.

Failures of intraperitoneal catheters can be corrected infrequently. Infected catheters should be removed and not replaced. Blocked catheters can be replaced if the patient has free intraperitoneal space remaining between bowel loops and has not had peritonitis as a complication of having undergone surgery or having received chemotherapy. Access problems attributable to a rotated port can be easily corrected. Most patients, however, resume their chemotherapy with treatment administered intravenously alone when catheter complications occur.

INTRAPERITONEAL CHEMOTHERAPY: WHICH REGIMEN?

The 2013 update of the NCCN Guidelines suggested an intraperitoneal regimen based on the experimental arm of GOG 172: cisplatin administered intraperitoneally 75 to 100 mg/m^2 and a 3-hour infusion of paclitaxel intravenously on day 1 with 60 mg/mg^2 delivered intraperitoneally on day 8. The reduced dose of cisplatin administered intraperitoneally (75 mg/m^2) was included because of concerns over the toxicity of 100 mg/m^2 with patients who did not complete the planned six cycles of intraperitoneal/intravenous therapy postsurgery. This dosing is also reflected in the experimental arms of both GOG 252 and OV21/PETROC.[44]

Given the toxicity associated with cisplatin and the emerging nonrandomized data on carboplatin administered intraperitoneally, some centers have adopted intraperitoneal carboplatin-based regimens.[45,46] Randomized data to better inform the selection of an intraperitoneal/intravenous regimen will be available soon from GOG 252 and OV21/PETROC. Given that GOG 172 demonstrated an OS benefit in an intention-to-treat analysis when the median number of cycles delivered was three (although the studies to date have looked at six cycles of chemotherapy), a question remains as to whether six is the optimal number of intraperitoneal treatments.[18]

When discussing chemotherapy options for patients whose disease is optimally cytoreduced, clinicians face the challenge of discussing three basic choices: (1) carboplatin and paclitaxel administered intravenously every 3 weeks (GOG 158, GOG 182), (2) carboplatin administered intravenously every 3 weeks with paclitaxel administered intravenously weekly (JGOG-3016, GOG 262), or (3) an intraperitoneal/intravenous regimen.[32,42,47,48] The subset of women with stage III optimally cytoreduced disease in ICON 7 did not derive benefit from the addition of bevacizumab to carboplatin and paclitaxel administered intravenously every 3 weeks.[49] Data from OV21/PETROC, GOG 252, and JGOG iPocc (NCT01506856) studies are eagerly awaited because they will provide information on the comparison of a dose-dense intravenous regimen with intraperitoneal/intravenous chemotherapy. This will address the question of dose density that remains from the GOG 172 data. The role of bevacizumab in combination with intraperitoneal/intravenous chemotherapy is being explored in GOG 252. The tolerability of the regimen was established in a previous phase II trial, although three bowel obstructions (7%) were observed.[50] Further safety data on the combination of bevacizumab and intraperitoneal/intravenous therapy will be available from GOG 252. GOG 262 is a study that compared carboplatin/paclitaxel administered intravenously every 3 weeks with carboplatin administered intravenously on day 1 with weekly dosing of paclitaxel intravenously. Bevacizumab was allowed as an (nonrandomized) option in both arms of the trial. This study demonstrated that dose-dense paclitaxel improve PFS over the dosing of paclitaxel every 3 weeks, but this was only true in women not receiving bevacizumab. The addition of bevacizumab appeared to eliminate the beneficial effects of dose-dense paclitaxel.[47] In GOG 252, bevacizumab is included on cycles 2–22, and the study was designed with the assumption that there would be no interaction between the various chemotherapy arms and bevacizumab, which would hide the effects of the individual chemotherapy regimens. The surprising results of GOG 262 raise concern that the addition of bevacizumab to all patients on GOG 252 may have obscured the effects of the individual chemotherapy regimens alone. Insufficient data exist at this time to recommend bevacizumab in combination with intraperitoneal/intravenous chemotherapy as a standard-of-care option. Results for GOG 252 are expected to be reported at the Society of Gynecologic Oncology meeting in March 2016.

Ultimately, the factors that patients and families should be empowered to consider when making decisions about adjuvant treatment will include convenience, potential toxicities, and quality of life in addition to the data on efficacy.

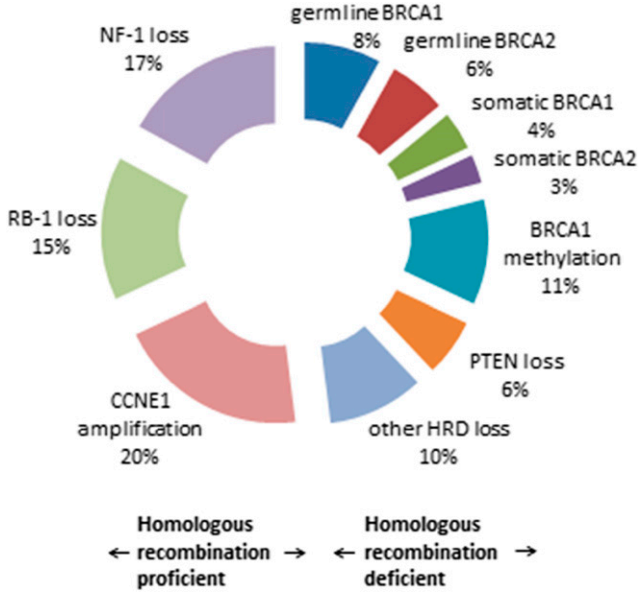
PATIENT SELECTION FOR INTRAPERITONEAL CHEMOTHERAPY

The last consideration is whether there are individual patient findings that should be factored into decisions regarding whether chemotherapy should be administered intraperitoneally/intravenously or just intravenously to patients. It is now clear that at the immunohistochemic level, epithelial ovarian cancer consists of at least five different diseases.[51-53] Although previous randomized studies of intraperitoneal/intravenous chemotherapy versus intravenous chemotherapy did not select or stratify on the basis of histologic subtype, it is now apparent that subtypes such as low-grade serous, low-grade mucinous, and clear cell are less sensitive to chemotherapy than high-grade serous or high-grade endometrioid ovarian cancer. The low likelihood of a considerable chemotherapy dose-response relationship in these less-sensitive subtypes makes it difficult to justify subjecting these patients to the additional toxicity of intraperitoneal chemotherapy. Rather, the main subgroup of patients who should be considered for intraperitoneal administration of chemotherapy are those with high-grade serous ovarian cancer (patients with high-grade endometrioid cancer are an under-researched subgroup), but what little evidence there is suggests they could be considered similar to high-grade serous from a biologic perspective).

Currently, given the strong evidence of benefit from GOG 114[21] and GOG172[18] studies, there is insufficient evidence to support any further patient selection based on biologic subtype in patients with optimally cytoreduced disease who have good performance status. However, the finding that patients from the GOG 172 study with low-tumor BRCA1 expression (as assessed by immunohistochemistry) appeared to benefit more from intraperitoneal/intravenous chemotherapy than intravenous chemotherapy (median survival 84 compared with 48 months, p = .0002) than those with normal BRCA1 expression (median survival 58 months for intraperitoneal chemotherapy compared with 50 months for intravenous chemotherapy) suggests that there are molecular subgroups that may benefit more from the intraperitoneal route of delivery.[54] The main molecular characteristics underlying high-grade serous ovarian cancer have recently been uncovered (Fig. 3).[51,55] Given the strong preclinical and clinical data supporting a high level of platinum sensitivity in BRCA1- and BRCA2-deficient ovarian cancer cells, it is not surprising that patients with low BRCA1 protein expression may derive particular benefit from administration of chemotherapy intraperitoneally. The question is whether this benefit applies only to tumors that carry germline or somatic *BRCA1* mutations, or whether those patients with epigenetic *BRCA1* inactivation, *BRCA2* mutations, *PTEN* loss, *EMSY* amplification, or mutations in other homologous recombination deficiency genes also derive benefit. Although BRCA1 immunohistochemistry analysis is notoriously inaccurate, the technology now exists to perform this other sequencing and copy number characterization on archival formalin-fixed, paraffin-embedded material. This retrospective analysis should be performed as a matter of urgency using material from randomized studies of intraperitoneal chemotherapy to demonstrate whether particular molecular subgroups have more to gain from intraperitoneal treatment. It is already clear that some molecular subgroups have a high incidence of primary platinum resistance (Fig. 3; homologous recombination proficient),[55,56] and these patients may not benefit from intraperitoneal therapy; instead, perhaps they should be considered for dose-dense paclitaxel and carboplatin administered intravenously, or trials of other novel therapies in combination with their first-line chemotherapy, to optimize survival and avoid unnecessary toxicity.

Although "cure" is a word that most ovarian cancer oncologists try to avoid, this must be our aim. The survival that has been demonstrated in patients with completely cytoreduced disease and who received intraperitoneal chemotherapy in the GOG172 study is a sea change in terms of what we expect in this disease. It reinforces the argument that in fit patients, maximal cytoreductive surgery followed by intraperitoneal chemotherapy is the treatment likely to produce the best possible outcome. However, the morbidity induced by both these treatments makes it even more imperative that we are able to define whether it is only patients with a particular biology (e.g., *BRCA* mutations or homologous recombination deficiency) that benefit. For these patients, "full-on" surgical/intraperitoneal chemotherapy with or without PARP maintenance inhibitors (depending on the outcome of currently running first-line PARP inhibitor studies) could be adopted. For the patients with different biology, alternative tailored approaches could be sought.

FIGURE 3. Molecular Subgroups of High-Grade Serous Epithelial Ovarian Cancer



Abbreviations: HRD, homologous recombination deficient.

CONCLUSION

Large randomized phase III studies have been ubiquitously positive, producing some of the best survival data ever seen in the treatment of ovarian cancer. However, all of these studies have had issues, either with the intravenous chemotherapy (control) arm being perceived as no longer contemporary or the intraperitoneal (test) arm having higher dose intensity than the control arm and, therefore, not being a trial solely of route of administration. These apparent shortcomings combined with undoubted toxicity of the approach have led to inconsistent uptake in North America and Australia and negligible uptake in Europe. This seems a shame given that the benefits in terms of outcome appear so marked. Indeed, the benefits are well in excess of those demonstrated in the first-line bevacizumab studies that led to licensing and reimbursement of this agent across Europe.

Further work is required to improve the toxicity from chemotherapy administered intraperitoneally and to identify the best regimen and determine the extent to which the benefits witnessed also can be produced by dose-dense approaches or the use of targeted agents. These latter two questions may be answered to some extent by the GOG252 study. Perhaps the most important question that requires to be answered is exactly which molecular subgroups of ovarian cancer patients benefit most from

intraperitoneal treatment. If this can be established, these patients may benefit greatly from an aggressive surgical and intraperitoneal chemotherapy approach. The question is, will this be enough to change practice?

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