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Proceedings of a GOG Workshop on Intraperitoneal Therapy for Ovarian Cancer

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Abstract

Ovarian cancer is the leading cause of gynecologic cancer deaths in the U.S. The concept of intraperitoneal drug delivery for therapy of intraperitoneal cancers, such as ovarian cancer, arose in the 1960s. The field of intraperitoneal cisplatin therapy for ovarian cancer was initiated in the late 1970s and early 1980s. The markedly improved survival data resulting from a third phase III trial of intraperitoneal cisplatin for ovarian cancer in early 2006 led to an NCI Clinical Announcement and a Gynecologic Oncology Group-sponsored workshop on Intraperitoneal Therapy in January, 2006, in San Diego, California. The proceedings of this workshop summarize both research trial results and practical implementation issues associated with intraperitoneal therapy discussed at this workshop.

Introduction

The concept of intraperitoneal drug delivery for therapy of intraperitoneal cancers, such as ovarian cancer, arose in the 1960s and was studied intensely by a group of bioengineers led by Dr. Robert Dedrick at the National Institutes of Health [1]. It was there that Dedrick and his colleagues described the pharmacokinetic and pharmacodynamic principles underlying modern intraperitoneal chemotherapy in animal and human models. These studies led to the development of “belly bath” chemotherapy regimens for ovarian cancer Speyer and research colleagues in the late 1970s at the National Cancer Institute, mainly focusing on antimetabolite type agents [2,3].

The field of intraperitoneal cisplatin therapy for ovarian cancer was initiated by Drs. Stephen Howell and Maurie Markman at the University of California-San Diego in the late 1970s and early 1980s [4]. They proved that cisplatin in doses of up to 100 mg/m² could be delivered into the intraperitoneal space in up to 2 liters saline, safely and effectively to women with optimally

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debulked, stage III ovarian cancer. In fact, they and others established that peak peritoneal fluid to peak plasma concentration ratios for doses of 90–100 mg/m² intraperitoneal cisplatin averaged about 20 and that the systemic absorption of intraperitoneal cisplatin approached the plasma concentration · time products obtained with the same doses administered intravenously [4,5].

Important pharmacokinetic principles of IP chemotherapy appear in Table 1. There is a well-documented inverse relationship between the molecular weight of an intraperitoneal drug and tumor penetration from its outer core (e.g. it requires 10 times more intraperitoneal carboplatin than intraperitoneal cisplatin to achieve similar intratumoral concentrations of platinum [6,7]. Additionally, there is an inverse relationship between the intraperitoneal drug fluid volume administered and its clearance rate from the intraperitoneal space. Thus, the large saline fluid volume used to administer intraperitoneal chemotherapy not only assures drug distribution throughout the intraperitoneal space, but also retards drug clearance to make a drug more available to intraperitoneal tumor deposits. Finally, as documented by Howell et al. and Casper et al.[4,5] with intraperitoneal cisplatin, and by Markman et al. and Francis, et al.[8,9] with intraperitoneal paclitaxel, large systemic plasma concentration · time products of intraperitoneal administered drugs can be achieved in the absence of relatively low peak plasma concentrations. As a result of the latter phenomenon, IP administered cisplatin is associated with considerably less tinnitus, hearing loss and neutropenia than the same doses administered intravenously [10].

Listed in Table 1 are basic concepts of intraperitoneal chemotherapy that have been challenged over the past 25 years. Nevertheless, they represent both past and current thinking concerning the advantage established in phase III trials for intraperitoneal therapy. Note that the use of an intravenous, rather than peritoneal catheter is recommended to avoid the development of fibroblast sheath formation that often occurs with the latter type catheter.

The following is derived from presentations made at a Gynecologic Oncology Group [11]-sponsored workshop on Intraperitoneal Therapy in January, 2006, in San Diego, California. The workshop was planned to follow the publication of the high impact survival data from GOG-172 and the publication of a National Cancer Institute Clinical Announcement [12,13], and to present both research trials and practical implementation issues.

SWOG-8501/GOG-104

Phase I and II trials in the 1980s of intraperitoneal cisplatin-based, second-line therapy for epithelial type, advanced ovarian cancer documented surgically defined complete responses and prolonged survival in a subset of patients [4,14–16]. SWOG-8501/GOG-104, “Intraperitoneal Cis-Platinum/Intravenous Cyclophosphamide *versus* Intravenous Cis-Platinum/Intravenous Cyclophosphamide in Patients with Non-Measurable (Optimal) Disease Stage III Ovarian Cancer,” was the first and largest phase III trial designed to test the hypothesis that intraperitoneal cisplatin as compared to intravenous cisplatin would prolong survival duration in women with stage III, optimally debulked ovarian cancer. This study was initiated as a collaborative effort by the GOG, the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG).

Six hundred fifty four (546) fully eligible patients were randomized to receive cisplatin 100 mg/m² either intraperitoneally or intravenously plus cyclophosphamide 600 mg/m² intravenously (both groups) on Day 1 of a 21-day cycle for 6 consecutive cycles. To be eligible, patients must have undergone bilateral salpingo-oophorectomy, total abdominal hysterectomy, partial omentectomy, para-aortic lymph node sampling and surgical resection of all residual tumor plaques ≥ 2 cm. Intraperitoneal cisplatin was administered in 2 liters normal saline with 1–2 liters normal saline plus 40 gm mannitol administered intravenously.

The median survival on the intraperitoneal cisplatin study arm was 49 months compared to 41 months on the intravenous cisplatin study arm ($p = 0.02$) (Table 2). The hazard ratio for overall survival was 0.76 (i.e. 24% reduction in the risk of mortality associated with intraperitoneal therapy). Progression-free survival was not calculated, because of the large proportion of patients who underwent second-look exploratory laparotomy and, therefore, required data censoring. Of those participants who had only microscopic residual disease after the initial exploratory laparotomy, 80% of those treated with intraperitoneal and 56% of those treated with intravenous cisplatin had histopathologically proven negative second-look surgery results.

In this study, patients randomized to receive intraperitoneal cisplatin experienced less toxicity than those treated with intravenous cisplatin. There was statistically significant difference between the treatment groups of $\geq$ grade 3 granulocytopenia (i.e. 56% versus 69%), moderate or severe tinnitus (i.e. 7% versus 14%) and moderate or severe clinical hearing loss (i.e. 5% versus 15%) in patients receiving intraperitoneal, as compared to those receiving intravenous cisplatin, respectively. Abdominal pain of $\geq$ grade 2 was significantly higher in the intraperitoneal cisplatin-treated patients, but this toxicity was short-lived (i.e. 4–6 hours). This acute toxicity is successfully treated in the majority of women with orally administered narcotics and is also highly correlated with the total amount of instilled intraperitoneal fluid volume.

After two decades of developing the preclinical pharmacology and performing phase I and II clinical trials of intraperitoneal therapy, SWOG-8501/GOG-104 was an important proof-of-principal phase III trial wherein the only difference in the chemotherapy regimens was the route for cisplatin administration (i.e. intraperitoneal versus intravenous). SWOG-8501/GOG-104 resulted in a median 8 month increase in survival duration and 24% reduction in mortality among those treated with the intraperitoneal regimen. Because the intraperitoneal cisplatin regimen is associated with much lower peak plasma concentrations of cisplatin, there was less myelotoxicity and clinical hearing loss experienced by the patients on the intraperitoneal study arm[17].

The results of this trial were presented initially at a plenary session of the American Society of Oncology in Los Angeles in 1995 and then published in the New England Journal of Medicine in 1996 [17]; however, with the advent of intravenous platinum plus paclitaxel regimens, this intraperitoneal cisplatin/intravenous cyclophosphamide regimen was never implemented into standard practice. Nevertheless, SWOG-8501/GOG-104 stands as a hallmark study in oncology, leading directly to the design of GOG-114 and GOG-172, which tested the same intraperitoneal dose of cisplatin (i.e., 100 mg/m²) added to paclitaxel, administered intravenously or intravenously and intraperitoneally, respectively[12,18].

GOG-114

Despite the demonstration of an overall survival benefit (49 months versus 41 months, $p = 0.02$) associated regional cisplatin delivery in S8501/GOG-104 [17], the substitution of intravenous paclitaxel for intravenous cyclophosphamide as the “second drug” in the ovarian cancer chemotherapy regimen was believed to achieve the same benefits observed with regional treatment[19]. However, a second possibility was that intraperitoneal cisplatin administration would enhance the activity of a paclitaxel-containing regimen, just as it had for a treatment regimen containing cyclophosphamide. This issue could only be resolved through the conduct of a second randomized phase III trial.

An additional issue of interest was whether it might be possible to enhance the demonstrated activity of the regional treatment program by further reducing the volume of intra-abdominal disease *prior to* the administration of intraperitoneal cisplatin. One method to potentially

accomplish this goal was to give several cycles of a moderately intense intravenous chemotherapy program before starting intraperitoneal drug delivery[20].

Thus, GOG 114 compared the “new standard” regimen of intravenous cisplatin (75 mg/m²) plus paclitaxel (135 mg/m² over 24 hours) to an “experimental program” of two cycles of intravenous carboplatin (AUC 9), followed by 6 cycles of intraperitoneal cisplatin (100 mg/m²) plus intravenous paclitaxel (135 mg/m² over 24 hours)[18].

While an interesting concept, the specific “chemical cytoreduction” regimen employed in this trial resulted in a very high incidence of severe, and persistent, bone marrow suppression (particularly thrombocytopenia), such that 19% of patients randomized to the regional treatment arm received two or fewer courses of intraperitoneal cisplatin[18].

Despite this fact, employing an “intent-to-treat” analysis, patients randomized to the experimental regimen of intraperitoneal cisplatin plus intravenous paclitaxel experienced a statistically-significant improvement in both progression-free survival (28 months versus 22 months, $p = 0.02$) and overall survival (63 months versus 52 months, $p = 0.05$). Of note, this was the first randomized trial in advanced ovarian cancer to reveal a median survival of more than 5 years for one of the treatment arms in the study.

The two courses of “moderately high dose” intravenous carboplatin were unlikely to have contributed in a meaningful way to the favorable results of this trial as a number of previously reported phase III trials have convincingly shown that platinum “dose-intensity,” at the systemic drug concentrations achieved in this study, does not improve outcome, but can substantially increase the toxicity of the treatment regimen[21,22].

The most important result of this second phase III trial, exploring the role of intraperitoneal chemotherapy as a primary management option in ovarian cancer, was the demonstration that regional cisplatin delivery *added to the benefits* achieved by substituting intravenous paclitaxel for intravenous cyclophosphamide.

GOG-172

The development and conduct of large, phase III studies are never completed in a vacuum, but are built upon prior and existing knowledge. GOG-172[12] was built on information gained from the previous phase III studies described above. In this study, 416 patients were randomized to receive intravenous (135 mg/m² intravenous paclitaxel over a 24-hour period on day 1 followed by 75 mg/m² intravenous cisplatin on day 2) or intraperitoneal (135 mg/m² intravenous paclitaxel over a 24-hour period on day 1 followed by 100 mg/m² intraperitoneal cisplatin on day 2 and 60 mg/m² intraperitoneal paclitaxel on day 8) chemotherapy. Patients receiving IP therapy experienced side effects with greater frequency and/or severity than those randomized to the IV regimen; these findings are likely due to the intensity of the dose on the IP arm. Patients receiving IP therapy experienced greater thrombocytopenia, neutropenia, and a higher infection rate (12 versus 4% for thrombocytopenia, 76 versus 64% for neutropenia, and 16 versus 5% for infection for IP versus IV therapy, respectively). Non-hematologic toxicities were also greater among those treated with IP therapy (46 versus 24% gastrointestinal toxicity, 19 versus 9% neurologic toxicity, 18 versus 4% fatigue, 27 versus 7% metabolic toxicity, and 11 versus 1% experiencing pain in the IP and IV treatment arms, respectively).

Only 42 percent of patients randomized to IP therapy completed all six cycles of assigned IP therapy compared to 83% in the IV arm completing assigned treatment. Most patients in both arms received six courses of assigned or other chemotherapy treatment (90% of patients randomized to IV therapy compared to 83% of patients randomized to IP therapy). Primary

reasons for discontinuation of IP therapy (n=119) included catheter complications (n=40, 33%), toxicity (n=31, 26%), and non-catheter issues such as patient refusal (n=19, 16%), non-catheter related infection (n=7, 6%), and other reasons (n=11, 9%)[23]. IP therapy was administered to 16% of patients randomized to IP therapy who had a left colon or rectosigmoid colon resection (compared to 4% of patients who did not, $p = 0.012$). No relationship was found between the timing of catheter insertion and subsequent failure to complete IP therapy[23].

There was a statistically significant improvement in progression-free survival associated with IP therapy (23.8 versus 18.3 months for IP versus IV therapy, relative risk [RR]: 0.80, $p=0.05$). There was also a 25% reduction in risk of death associated with IP therapy (RR: 0.75, $p=0.03$), with an overall survival of 65.6 months in the IP arm versus 49.7 months in the IV arm. When looking at survival by subgroup, IP therapy was found to be beneficial both for patients with visible disease (about 2/3 of patients) and for patients with microscopic disease, with overall survival relative risk of 0.77 and 0.69, respectively. When looking at negative second look rates in GOG-172 and other GOG studies in optimal ovarian cancer (GOG-104, GOG-158 [24], and GOG-172), the negative second look rate in the IP arm in GOG-104 was 47% as compared to the 57% negative second look rate in the IP arm of GOG-172. The intravenous treatment groups from these studies showed a 36% negative second look rate in GOG-104, 46% in GOG-158, and a comparable 41% in GOG-172. Second-look data are not available from GOG-114. When comparing progression-free survival among these studies, it is noted that this has actually declined over time (for IV therapy: 22.2 months in GOG-114, 19.4 in GOG-158, and 18.3 months in GOG-172; for IP therapy: 27.9 months in GOG-114 and 23.8 months in GOG-172). However, caution must be taken when directly comparing progression-free survival between these trials; it must be taken into consideration that definitions of progression have changed over time. Currently, CA-125 is used to define progression in GOG trials, unlike the PET scans and imaging requirements of the prior studies. Nevertheless, in overall survival, there has been a sequential improvement over time (IV therapy: 41 months in GOG-104, 52.2 months in GOG-114, 57.4 months in GOG-158, and 49.7 months in GOG-172; IP therapy: 49 months in GOG-104, 63.2 months in GOG-114, and 65.6 months in GOG-172).

In conclusion, the IP regimen used in GOG-172 used a higher and more frequent dosing schedule than the IV regimen. This in part contributes to the greater toxicities experienced among patients randomized to IP therapy, and fewer patients on the IP arm were able to complete 6 cycles of therapy. There was also a statistically significant improvement in both progression-free and overall survival for patients randomized to the IP arm. The 65.6 month median survival on the IP arm is the longest survival reported to date from a randomized trial in advanced ovarian cancer and represents the advancements in survival from ovarian cancer that are being made possible from these sequential studies.

New Chemotherapy Regimens

The results of randomized trials of IP therapy in ovarian cancer suggest that IP cisplatin leads to more efficient control of peritoneal disease, and, in turn, this impacts on survival—presumably by lessening life-threatening peritoneal recurrences. In fact, Howell and co-workers at UCSD had first reported a highly favorable survival experience when IP cisplatin was used as consolidation, thus generating much enthusiasm in the 1980s[14]. The EORTC (European Organization for Research and Treatment of Cancer) studied IP cisplatin consolidation versus observation after negative second-look laparotomies, but closure due to poor accrual precluded drawing firm conclusions[25]. One would have predicted that such IP consolidation (i.e., after IV induction) would result in an improved outcome, unless platinum resistance has already supervened. In considering regimens for IP consolidation, therefore, we have thought it desirable to add other agents to IP cisplatin—especially if there is residual

disease. The basis for selection of IP drugs, previously studied regimens, and a new cisplatin + topotecan regimen are here described.

The integration of new IP regimens into phase III clinical trials requires detailed prior phase I and pharmacologic studies, so that tolerance by the peritoneum, avoidance of catheter complications, and their potential contributions to systemic control of disease and systemic toxicity are well defined. Pharmacologic advantage (i.e., the ratio of AUC in peritoneal cavity/AUC in plasma) may be less important than tissue penetrance—a parameter dependent on molecular weight of the drug in question—and whether suitable plasma levels are achieved (an issue with IP *paclitaxel*, thus the need for IV administration). Activity against the disease in question is a key basis for selection; however, 5-day IP *cytarabine* led to complete responses while lacking activity given IV [14,26]. IP *carboplatin* yielded satisfactory results by itself and in combination with IP *etoposide* [27,28]. *FUDR*, developed initially as IP consolidation for gastrointestinal cancer, was chosen for further study in a ‘pick the winner’ design in SWOG-8835 that also tested IP *mitoxantrone* for consolidation following positive reassessment in ovarian cancer [29]. Subsequently, IP *FUDR* was given in combination with IP cisplatin and/or carboplatin [30] and other IP platinum-containing regimens were tested building on Howell’s initial experience [31], but limited conclusions can be drawn from non-randomized trials. Other cytotoxic drugs of current interest for IP study are *gemcitabine* and *docetaxel*.

Low volume (< 1cm) residual disease and usually specified adequate organ function were required. A Port-A-Cath device for repeated IP administration was placed at laparotomy or laparoscopy within 8 weeks of IP therapy. The first dose level consisted of IP topotecan at a dose of 1.5 mg (not per meter square) for 5 days given every 21 days for 6 cycles (Table 3). At subsequent levels, on day 1 IP cisplatin 50 mg/m² in 1L NS was given preceded by IV HT3 antiemetics and prehydration (1L of NS with 2 grams of magnesium sulfate and 20meq KCL at 200ml/hr). Post hydration and antiemetics were also often given. Immediately after, topotecan was delivered IP in 500ml NS followed by repeated delivery in 1.5–2L on subsequent days; oral antiemetics were used on days 2 and 3. Dose-limiting toxicities (DLTs) were defined as grade 3 nonhematologic toxicity or any grade 4 toxicity based on the first 2 cycles. Dose modifications were made for grade 3 or 4 neutropenia and/or thrombocytopenia (reduction by 1 dose level). A creatinine > 1.8 mg and/or grade ≥ 3 neuropathy required dose reduction of cisplatin by 50% (for reversible toxicity) or omission (if not reversible).

Fifteen patients were enrolled with stage III epithelial ovarian or tubal cancer after prior carboplatin or cisplatin induction (Table 4). Myelosuppression occurred at all doses that included cisplatin: at dose level 1, 3 of 4 patients developed grade ≥3 neutropenia (2 grade 4) after cycle 1 between days 21–24 (median ANC nadir 814), necessitating a one week dose delay in all three. Due to these findings, dose level 2 was introduced reducing topotecan to 1.25 mg on days one through three, and this was found tolerable. At dose level 3, however, four of five patients developed grade ≥3 neutropenia on C2D19, C1D17, C1D15, C1D17 (median ANC nadir 854). Nonhematologic toxicities were mild, although two creatinine elevations just beyond 2 mg were noted; one patient experienced fever and abdominal pain while receiving her 5th cycle.

Consolidation therapy after platinum-based induction and planned surgical reassessment was given to six patients after positive and three patients after negative reassessments. Progression was defined by physical examination, imaging, new development of positive cytology, and/or marked rises in CA-125 (> 100% above a baseline of > 35 units). At the conclusion of the study, only two of these nine patients had progression at six weeks and 57 weeks from onset of treatment [32]; analysis of progression-free survival (PFS) awaits further update. Six patients were treated either after secondary debulking (four patients) or after recurrence from prior IP

consolidation based on cytology (two patients). Progression occurred at 15, 16, 23, 38, and 86 weeks, with one patient in remission at 54+ weeks. CA-125 decreased by 20 to 78% in four of four patients (100%) with an abnormal marker baseline.

Serial peritoneal and plasma samples for total topotecan (Table 5) were obtained during either the first or 2nd cycle on nine patients (three patients each at levels 0, 1, and 3); levels were measured by high performance liquid chromatography (HPLC) as published [32,33]. Range for peak IP and plasma levels were 208–679 ng/ml and 6–23 ng/ml, respectively; IP/plasma AUC ratios ranged from 24–110.

Cisplatin followed by topotecan yields synergy [34]. Topotecan is non-vesicant, and its active lactone form is favored in an acid pH [35]. Muntz et al treated 23 women with IP topotecan 20 mg/m² every 3 weeks as consolidation after positive reassessment and report 70% progression-free, at a median follow-up of 18 months[36]. A case could be made for intraperitoneal consolidation after a negative reassessment randomizing to IP cisplatin or IP cisplatin + topotecan. After positive reassessments, a comparison of two non-platinum containing drugs (such as was done in SWOG8835) might further enable the identification of promising IP regimens.

Issues in Patient Selection

Unique patient characteristics must always be considered in the decision to employ an intraperitoneal chemotherapy strategy. For example, a patient with ovarian cancer who is to receive intraperitoneal cisplatin must have adequate renal function, as appropriately required for systemic delivery of this agent. Similarly, an individual with a baseline significant symptomatic peripheral neuropathy (e.g., diabetes-associated) may not be a good candidate to receive this agent delivered either intraperitoneally or intravenously.

Patients with known significant peritoneal adhesions, perhaps from a prior serious intra-abdominal infection, may not be able to receive regional treatment, despite otherwise being in a clinical setting where intraperitoneal drug delivery has revealed a major survival advantage compared to systemic drug delivery.

Further, patients with ongoing abdominal infections, or where the indwelling intraperitoneal catheter becomes infected or malfunctions, will be unable to be treated by this route of drug delivery.

There is also the important issue of the size of residual tumor masses that should declare an individual patient to be a poor candidate for intraperitoneal treatment.

While pre-clinical evaluation has clearly demonstrated the limited *direct penetration* of antineoplastic agents into tumor (or normal) tissue [6,37], and experience with second-line intraperitoneal treatment of ovarian cancer clearly indicates patients with the smallest volume of residual disease (microscopic cancer only or macroscopic nodules < 0.5 cm in maximum diameter) are far more likely to achieve biological evidence of a response to this therapeutic approach [15], it would appear to be inappropriate to conclude patients being considered for a primary intraperitoneal chemotherapy approach should be required to have tumor masses of this size.

The justification of this statement is as follows: Following intraperitoneal cisplatin delivery, systemic levels of the drug comparable to that achieved with intravenous delivery will be achieved. As the large majority of ovarian cancer patients receiving primary chemotherapy will be anticipated to respond to this agent, there is likely to be substantial reduction in the size of any residual tumor nodules at the time of the second or third intraperitoneal treatment cycles,

permitting a larger portion of the residual cancer to be exposed to the high drug concentrations present (10 to 20- fold for cisplatin; 1000-fold for paclitaxel) within the infused treatment volume.

Thus, a “2-cm” mass, present when the first cycle of intraperitoneal cisplatin is delivered, is likely to be a much smaller nodule (or even microscopic disease only), when the second course is administered, three weeks later.

Nursing Perspectives

Intraperitoneal [9] chemotherapy can be an intimidating procedure for both patients and nurses. With a good review of the procedures and guidelines, it can be an enjoyable and rewarding experience for everyone involved.

Education is the key to creating a positive IP chemotherapy experience. There are many details to explain about IP chemotherapy; therefore, it is beneficial to begin this education process with the patient prior to the surgical procedure. The patient and family will then have sufficient time to process decision options. Early discussions also help to establish a relationship between patient and physician that will foster a positive decision-making experience throughout the treatment period. Written and verbal instructions will help standardize education for all patients and ensure that all necessary information is readily available. Patients find it useful to have written instructions at home to use as reference guide to answer questions as they arise.

The diagnosis of cancer, coupled with the need for surgery and chemotherapy, can be overwhelming. Many women feel powerless in this situation. It is possible to restore a patient's sense of control by providing emotional support from the time of diagnosis through and following the treatment period. Encouraging patients to meet and talk with others who have received IP chemotherapy may help patients receive firsthand knowledge on what they may experience during treatment. Sometimes it just takes hearing from someone who had treatment, and tolerated it well, to alleviate fears and make the decision process easier. Contact numbers for both the physician and nurse should be provided so patients and their families have access to someone who is knowledgeable when questions arise.

The first question that typically arises is how to access the abdomen. There are two approaches to accessing the peritoneal cavity: implanted devices, such as mediports; or external devices, such as Groshong or Tenckhoff catheters. Most physicians choose to use an implanted device because it is easier for the patient to care for at home than an external device. IP devices are accessed using aseptic technique. It is important to use a needle that is long enough to safely access the port (typically 1.5–2.0 inches) due to the variability in abdomen size. The longer length needle helps to prevent infiltration and increases ease of administration of IP fluids. Following treatment, it is essential to educate patients about the signs and symptoms of infection specific to the peritoneal access device.

When a patient is scheduled for intraperitoneal therapy, it is useful to have experienced staff readily available to both facilitate a learning environment for any new staff, as well as to provide an uneventful experience for the patient. Patients should be reminded that they will feel bloated for several days after the IP infusion, and that this is a time when elastic pants will be more comfortable. When the patient arrives, she should be asked to describe any complaints that she has had between infusions. This enables the administration nurse to establish ongoing rapport with the patient. This relationship is important to help the nurse identify subtle changes that may forewarn of a potential future event. Medications should be reviewed and recorded at each course to keep a complete and thorough record. This will help to prevent allergic reactions or medication interactions. To ease a patient's anxiety, nurses should review all potential expected

and new side effects. This review helps the patient communicate what she is feeling and reduces unease associated with expressing concerns.

A strong antiemetic regimen that assures coverage over at least five days to prevent cisplatin-induced nausea and emesis. Pretreatment with IV Palonosetron (Aloxi) plus oral aprepitant (Emend) with IV dexamethasone (at least 20 mg) should be considered. Dexamethasone 4 mg orally each morning for at least five days with tapering of dose on days 6 and 7 post day-1 cisplatin should be considered.

Administering IP chemotherapy requires careful attention to several important details. Orders should be typed to insure that they are clear, concise and easy to follow. Typed orders also decrease administration errors and reduce questions during infusions. Any fluids that are to be infused into the peritoneal space must be warmed prior to infusion. This helps decrease side effects (e.g. cramping, burning, and pain). The method to do this will vary by institution, but usually involve using K-packs, blood warmers or warming in the sink. In addition to the IP port, patients will need peripheral IV access for premedications, hydration, antiemetics, and potentially for rapid administration of rescue medication if a hypersensitivity reaction occurs. Two liters of fluid will be infused into the abdomen prior to chemotherapy, bathing the entire peritoneal surface.

IV pumps should not be used and there should not be a blood return. Infusion times can vary between patients due to differences in body size and placement of access device. It can be helpful to place the patient in Trendelenberg position. Sluggish flow can often be improved by re-accessing and flushing the device; however, if these interventions do not improve the infusion rate, or if the patient experiences sharp pain, the attending physician should be called. It is extremely important for the nurse to be aware of how the patient is feeling and to be aware of any subtle complaints/changes in the patient's status.

Mild complaints of pain can be managed with narcotics. Orders for both IV and oral pain medications should be standard so these complaints can be addressed quickly. If the patient does experience acute or sharp pain, the infusion should be stopped and the attending physician should be called immediately. A dye study may be ordered to assess patency of the access device, and until patency is established, chemotherapy should be given through a peripheral line. At the conclusion of the IP infusion, patients may begin a "turning protocol." This protocol should be clearly described in the chemotherapy order, and typically varies from one-and-a-half to two hours. If intraperitoneal fluid volumes are in the range of 1.5 to 2 liters, then it is unlikely that a "turning protocol" is of any value, because good drug distribution will be assured. Prior to discharge, all signs and symptoms of infection must be reviewed with the patient, along with any issues that necessitate calling the doctor.

IP chemotherapy is sometimes an intimidating treatment option. It is imperative that that medical and nursing staff continue to support each other and their patients. Education of patients and staff will help to alleviate fears and increase confidence in the procedure. As this treatment choice becomes readily available, patients and doctors will want to employ IP chemotherapy as an important weapon in their fight against cancer.

Perspectives of the U.S. National Cancer Institute

The NCI and its investigators share an obligation to disseminate to the medical profession and the public the most significant results of federally supported clinical investigation as rapidly and effectively as possible. One mechanism used by the NCI in this process of dissemination is called a "Clinical Announcement", which NCI uses to bring new information of unusual importance to the attention of clinicians and patients. A NCI Clinical Announcement is not be construed as an authoritative directive dictating specific therapy for all patients. It is an

educational document, presented facts and formed opinions on options to be considered by physicians and patients.

NCI considers a Clinical Announcement when a clinical trial or trials have identified an intervention which substantially improves the survival outcome for a significant number of people with reasonable certainty and when that intervention is available to the general public. Past NCI Clinical Announcements focused on adjuvant systemic therapy for women with node-negative breast cancer (1988), the efficacy and group C status of levamisole and 5-fluorouracil for patients with Dukes' C colon cancer (1989), the adjuvant therapy of rectal cancer (1989), the adjuvant therapy of breast cancer (tamoxifen update, 1995), and concurrent chemoradiation for women with cervical cancer (1999).

In accordance with NCI guidelines, the data on IP chemotherapy in ovarian cancer was first reviewed by a panel of independent experts, including gynecologic oncologists, medical oncologists, biostatisticians, and patient advocates, jointly nominated by the Clinical Trials Cooperative Groups conducting the largest trials, namely the Gynecologic Oncology Group [11], the Southwestern Oncology Group, and the European Organization for Research and Treatment of Cancer Gynaecological Cancer Group, and the NCI. After review of the data, the panel recommended to the Director of the NCI that such a Clinical Announcement be issued. The text of the proposed Clinical Announcement was then reviewed by the panel, as well as the United States Food and Drug Administration, Bristol Myers Squibb, which had co-sponsored two of the trials, and the Office of the Director, National Institutes of Health.

On January 5, 2006, the National Cancer Institute issued a Clinical Announcement [38] recommending that women with stage III ovarian cancer, who undergo optimal surgical cytoreduction, be considered for IP chemotherapy. The Clinical Announcement was timed to coincide with the publication of the primary manuscript in the New England Journal of Medicine [12] and the secondary manuscript, on catheter outcomes, in Gynecologic Oncology [23].

The NCI has undertaken a broad-based dissemination and educational plan, in conjunction with the relevant professional societies, the NCI-designated Cancer Centers, the Clinical Trials Cooperative Groups who conducted these trials, and cancer advocacy groups. We welcome the help and expertise, for example, of the Society of Gynecologic Oncologists, the Gynecologic Cancer Foundation (GCF), the American Society of Clinical Oncology, the Society of Surgical Oncology, the American College of Obstetricians and Gynecologists, the Oncology Nursing Society, the Society of Gynecologic Nurse Oncologists, and the wide array of ovarian cancer advocacy groups brought together through the GCF's Allied Support Group and the Ovarian Cancer National Alliance.

Focus groups of doctors and nurses active in the care of women with ovarian cancer have made clear the importance of specific guidance on how to place IP ports, administer chemotherapy via an IP route, and manage expected toxicities. Such guidance is now available on the website of the GOG [11]. Through the Gynecologic Cancer Intergroup we have worked to make these research findings and the NCI Clinical Announcement available outside the United States [39]. We have also begun to plan how best to evaluate use of IP therapy as part of the standard management of women with optimally debulked stage III ovarian cancer in practices across the U.S. over the next few years.

The further development of IP therapy for women with ovarian cancer provides numerous research challenges. We need to investigate how to reduce the toxicity of IP administration while maintaining efficacy, how to combine an IP approach with new chemotherapeutic and biologic agents, as well as to gain a better understanding of the biologic mechanisms by which IP therapy improves cancer control. In addition, we need to determine the benefit of IP

administration in the consolidation setting, or after neoadjuvant chemotherapy followed by optimal cytoreductive surgery. While this research continues, however, we have a responsibility to ensure that women with advanced ovarian cancer who are candidates for IP therapy benefit from this treatment advance associated with such a remarkable improvement in overall survival.

Alternative Perspectives of the Benefit of IP therapy

The NCI's clinical announcement recently recommended that "consideration should be given to a regimen containing IP cisplatin (100 mg/m²) and a taxane" in patients with optimal stage III ovarian cancer[40]. The results of Gynecologic Oncology Group [11] protocol 172 were the primary basis for this recommendation[12]. GOG-172, GOG-114[18] as well as the NCI alert may overestimate the benefit of IP therapy in this group of patients. There has been no prospective randomized trial comparing IP therapy with intravenous (IV) carboplatin/paclitaxel, which is universally recognized as the standard of care against which all new treatment regimens should be compared[41].

GOG-158 compared IV carboplatin/paclitaxel with IV cisplatin/paclitaxel in 792 patients with optimal stage III ovarian cancer[24]. Median progression-free survival and overall survival were 19.4 and 40.7 months for patients treated with cisplatin/paclitaxel compared with 20.7 and 57.4 months for patients treated with carboplatin/paclitaxel. The relative risk (RR) of progression for carboplatin/paclitaxel was 0.88 (95% C.I. 0.75–1.03) and the RR of death was 0.84 (95% C.I. 0.70–1.02). GOG-114 and GOG-172 compared IP regimens with IV cisplatin/paclitaxel instead of carboplatin/paclitaxel. It has been suggested that carboplatin/paclitaxel and cisplatin/paclitaxel produce identical results in ovarian cancer and that the results of GOG-172 would have been the same even if the carboplatin/paclitaxel had been the comparative arm. There have been three randomized trials comparing carboplatin/paclitaxel versus cisplatin/paclitaxel in ovarian cancer. The first of these was an exploratory pilot study in stage II–IV ovarian cancer patients (both optimal and suboptimal), which was not intended as a definitive comparison due to the small numbers of patients entered[42]. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) trial also included stage II–IV disease[43]. While equivalency was demonstrated in this trial between these two combinations in the overall population of 798 patients, in a subset of optimally debulked patients there was an improvement in survival of 4 months (59.4 versus 55.4, RR 0.92 [C.I. 0.7–1.2]) for patients treated with carboplatin/paclitaxel. GOG-158, in which there was a trend toward improvement in survival for patients treated with carboplatin/paclitaxel, was the only trial exclusively in patients with optimally debulked ovarian cancer. This study, which reported an improvement in median survival of 8.7 months for patients treated with carboplatin/paclitaxel, together with a subset analysis of the AGO trial, indicate that there may be a significant improvement in survival for optimal stage III patients treated with carboplatin/paclitaxel compared to cisplatin/paclitaxel. Consequently, IP chemotherapy should have been compared to IV carboplatin/paclitaxel before any recommendations were forthcoming.

Table 6 provides a cross-trial comparison of carboplatin/paclitaxel in GOG-158 (n = 392) with IP therapy in GOG-172 (n = 206). It should be pointed out that these were sequential protocols performed in rapid sequence by the same group of investigators over a relatively short time span with identical eligibility criteria in both studies. Instead of the 5.5-month difference in progression-free survival and 15.9-month difference in overall median survival as reported for IP therapy compared to IV cisplatin/paclitaxel, when the results are compared with IV carboplatin/paclitaxel, the difference may be significantly less: 3.1 months for progression-free survival and 8.2 months for overall survival. Furthermore, when comparing the published survival curves between IP therapy on GOG-172 and IV carboplatin/paclitaxel on GOG-158, there is no difference in two-year survival and only a 4–5% difference in four-year survival.

An even better comparison than median survival and survival at any individual time point is the relative risk between the actuarial survival curves. From the shape of the published survival curves, it does not appear that there is a clinically significant improvement in survival for patients treated with the IP regimen. It should also be pointed out that 18% of patients randomized to IP therapy on GOG-172 received IV carboplatin/paclitaxel after discontinuing IP therapy due to excessive toxicity.[12] Cross-trial comparisons are not definitive, but are hypothesis generating. However, the strengths of this comparison are due to the large number of patients treated on sequential protocols, which used identical eligibility criteria and in which the control arm of IV cisplatin/paclitaxel produced identical results.

There are major differences in toxicities between IV carboplatin/paclitaxel and IP therapy. Standard therapy with IV carboplatin/paclitaxel consists of six outpatient administrations. In GOG-158, 87% of patients completed all six cycles[24]. In contrast, only 42% of patients on GOG-172 could complete six cycles of therapy[12]. As noted in the NCI alert,[40] patients treated with IP therapy are more likely to have infection and fever, abdominal pain, nausea and vomiting, and increased neurologic toxicity compared to patients treated with IV therapy. IP chemotherapy in GOG-172 consisted of a 24-hour infusion of paclitaxel followed by IP cisplatin on day 2 together with hydration, antiemetics, and more IP therapy with paclitaxel on day 8. This is in marked contrast to the six cycles of outpatient therapy with IV carboplatin/paclitaxel. While quality of life during therapy was significantly worse with IP therapy, there was no difference in quality of life one year later when compared with those patients treated with IV cisplatin/paclitaxel[44]. However, carboplatin/paclitaxel is a much less toxic regimen than cisplatin/paclitaxel, and this quality of life analysis underestimates the toxicity differences between IP therapy and standard IV carboplatin/paclitaxel.

Any new therapy should be prospectively compared against the existing best treatment available before it can be considered to be standard. In a recent consensus conference of clinical investigators from cooperative groups throughout the world, carboplatin/paclitaxel was recognized as the standard of care against which all new treatments should be compared[41]. There has been no IP regimen that has been directly compared with IV carboplatin/paclitaxel. Furthermore, even for those who advocate the routine use of IP chemotherapy in patients with optimal stage III disease, there is no consensus with regard to what constitutes an acceptable regimen[40]. The GOG is conducting phase I trials of new IP combinations in an effort to develop an IP regimen with acceptable toxicity. Until a well-controlled prospective randomized trial demonstrates a survival advantage of an IP regimen with acceptable toxicity, IV carboplatin/paclitaxel remains the standard of care for patients with optimal stage III disease.

Conclusions

This workshop brought together a number of important issues with regard to intraperitoneal chemotherapy. Although controversies do persist, and the optimal dose and schedule remains to be determined, there is consistent, statistically significant evidence to the survival benefit of intraperitoneal chemotherapy. The median overall survival of women treated with IP therapy on these trials has increased by about 17 months as we have improved this treatment regimen. Survival has increased from 49 months (S8501/GOG-104), to 63.2 months (GOG-114) and most recently to 65.6 months (GOG-172) with IP therapy as compared to standard IV carboplatin/taxol treatment survival (57.4 months, GOG-158). This improvement in survival has also corresponded with a similar quality of life one year following treatment as those receiving IV therapy[44]. The choice to receive or not receive IP therapy should be a decision made by the informed patient.

References

1. Dedrick RL, et al. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978;62(1):1–11. [PubMed: 626987]
2. Speyer JL, et al. Phase I and pharmacological studies of 5-fluorouracil administered intraperitoneally. *Cancer Res* 1980;40(3):567–72. [PubMed: 7471076]
3. Speyer JL, Myers CE. The use of peritoneal dialysis for delivery of chemotherapy to intraperitoneal malignancies. *Recent Results Cancer Res* 1980;74:264–9. [PubMed: 7444143]
4. Howell SB, et al. Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med* 1982;97(6):845–51. [PubMed: 6890785]
5. Casper ES, et al. Ip cisplatin in patients with malignant ascites: pharmacokinetic evaluation and comparison with the iv route. *Cancer Treat Rep* 1983;67(3):235–8. [PubMed: 6682012]
6. Los G, et al. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res* 1989;49(12):3380–4. [PubMed: 2720692]
7. Los G, et al. A rationale for carboplatin treatment and abdominal hyperthermia in cancers restricted to the peritoneal cavity. *Cancer Res* 1992;52(5):1252–8. [PubMed: 1737387]
8. Francis P, et al. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot Study. *J Clin Oncol* 1995;13(12):2961–7. [PubMed: 8523061]
9. Markman M, et al. Phase I trial of intraperitoneal taxol: a Gynecologic Oncology Group study. *J Clin Oncol* 1992;10(9):1485–91. [PubMed: 1355523]
10. Alberts DS, et al. Intraperitoneal therapy for stage III ovarian cancer: a therapy whose time has come! *J Clin Oncol* 2002;20(19):3944–6. [PubMed: 12351590]
11. GOG. IP Chemotherapy: Educational Materials. 2006 [Accessed April 6, 2006]. Available at: <http://www.gog.org/ipchemoed/ipchemoed.html>
12. Armstrong DK, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354(1):34–43. [PubMed: 16394300]
13. Trimble EL, Christian MC. Intraperitoneal chemotherapy for women with advanced epithelial ovarian carcinoma. *Gynecol Oncol* 2006;100(1):3–4. [PubMed: 16368439]
14. Howell SB, et al. Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. *J Clin Oncol* 1987;5(10):1607–12. [PubMed: 2443622]
15. Markman M, et al. Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: influence of a prior response to intravenous cisplatin. *J Clin Oncol* 1991;9(10):1801–5. [PubMed: 1919630]
16. Markman M, et al. Impact on survival of surgically defined favorable responses to salvage intraperitoneal chemotherapy in small-volume residual ovarian cancer. *J Clin Oncol* 1992;10(9):1479–84. [PubMed: 1517791]
17. Alberts DS, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;335(26):1950–5. [PubMed: 8960474]
18. Markman M, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19(4):1001–7. [PubMed: 11181662]
19. McGuire WP, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334(1):1–6. [PubMed: 7494563]
20. Shapiro F, et al. High-intensity intravenous cyclophosphamide and cisplatin, interim surgical debulking, and intraperitoneal cisplatin in advanced ovarian carcinoma: a pilot trial with ten-year follow-up. *Gynecol Oncol* 1997;67(1):39–45. [PubMed: 9345354]
21. Gore M, et al. Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. *J Clin Oncol* 1998;16(7):2426–34. [PubMed: 9667260]

22. McGuire WP, et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 1995;13(7):1589–99. [PubMed: 7602348]
23. Walker JL, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2006;100(1):27–32. [PubMed: 16368440]
24. Ozols RF, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21(17):3194–200. [PubMed: 12860964]
25. Piccart MJ, et al. Intraperitoneal cisplatin versus no further treatment: 8-year results of EORTC 55875, a randomized phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based intravenous chemotherapy. *Int J Gynecol Cancer* 2003;13(Suppl 2):196–203. [PubMed: 14656280]
26. Markman M, et al. Combination intraperitoneal chemotherapy with cisplatin, cytarabine, and doxorubicin for refractory ovarian carcinoma and other malignancies principally confined to the peritoneal cavity. *J Clin Oncol* 1984;2(12):1321–6. [PubMed: 6542584]
27. Muggia FM, et al. Intraperitoneal carboplatin and etoposide for persistent epithelial ovarian cancer: analysis of results by prior sensitivity to platinum-based regimens. *Gynecol Oncol* 1993;50(2):232–8. [PubMed: 8375739]
28. Speyer JL, et al. Intraperitoneal carboplatin: favorable results in women with minimal residual ovarian cancer after cisplatin therapy. *J Clin Oncol* 1990;8(8):1335–41. [PubMed: 2199620]
29. Muggia FM, et al. Intraperitoneal mitoxantrone or floxuridine: effects on time-to-failure and survival in patients with minimal residual ovarian cancer after second-look laparotomy--a randomized phase II study by the Southwest Oncology Group. *Gynecol Oncol* 1996;61(3):395–402. [PubMed: 8641622]
30. Muggia FM, et al. Phase I/II study of intraperitoneal floxuridine and platinum (cisplatin and/or carboplatin). *Gynecol Oncol* 1997;66(2):290–4. [PubMed: 9264578]
31. Barakat RR, et al. Intraperitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. *J Clin Oncol* 2002;20(3):694–8. [PubMed: 11821450]
32. Hochster H, et al. Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy. New York Gynecologic Oncology Group. *J Clin Oncol* 1999;17(8):2553–61. [PubMed: 10561322]
33. Mirchandani D, et al. Phase I study of combined pegylated liposomal doxorubicin with protracted daily topotecan for ovarian cancer. *Clin Cancer Res* 2005;11(16):5912–9. [PubMed: 16115933]
34. Rowinsky EK, et al. Sequences of topotecan and cisplatin: phase I, pharmacologic, and in vitro studies to examine sequence dependence. *J Clin Oncol* 1996;14(12):3074–84. [PubMed: 8955652]
35. O'Leary J, Muggia FM. Camptothecins: a review of their development and schedules of administration. *Eur J Cancer* 1998;34(10):1500–8. [PubMed: 9893620]
36. Muntz H, McGonigle K, Malpass T, Robertson M, Kamarauskiene D, Weiden P. Intraperitoneal topotecan as consolidation therapy for advanced ovarian cancer: results of a phase II study. The Chemotherapy Foundation. 2005 November 2–5;
37. Ozols RF, et al. Pharmacokinetics of adriamycin and tissue penetration in murine ovarian cancer. *Cancer Res* 1979;39(8):3209–14. [PubMed: 455305]
38. Trimble, E. NCI Clinical Announcement on Intraperitoneal Chemotherapy in Ovarian Cancer (January 5, 2006). 2006. Available at <http://ctep.cancer.gov/highlights/ovarian.html>
39. NCI. Intraperitoneal Chemotherapy for Advanced Ovarian Cancer. 2006 [Accessed April 6, 2006]. Available at: <http://ctep.cancer.gov/resources/gcig/>
40. NCI. NCI Clinical Announcement on Intraperitoneal Chemotherapy in Ovarian Cancer (January 5, 2006). 2006. Available at <http://ctep.cancer.gov/highlights/ovarian.html>
41. du Bois A, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 2005;16(Suppl 8):viii7–viii12. [PubMed: 16239238]
42. Neijt JP, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol* 2000;18(17):3084–92. [PubMed: 10963636]
43. du Bois A, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95(17):1320–9. [PubMed: 12953086]

44. Wenzel LB, Huang H, Armstrong D, Walker J, Cella D. Quality of life (QOL) results of a randomized study of intravenous (IV) paclitaxel and cisplatin vs IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): A Gynecologic Oncology Group trial. *Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings 2004;22(14S): 5028. July 15 Supplement

Table 1**Basic Concepts Underlying the Efficacy of Intraperitoneal [9] Chemotherapy Concepts Defended**

-
- IP chemotherapy treats both intraperitoneal tumor bed and extraperitoneal tumor through systemic recirculation (1, 4, 5, 8, 9)
 - IP chemotherapy achieves dose intensification in the intraperitoneal space of 20–1,000 fold that achieved with “high-dose” intravenous chemotherapy regimens (4, 5, 8, 9)
 - IP chemotherapy reaches intraperitoneal sites that may not be reached by the intravenous route, especially when up to 2 L of dialysate are administered
 - IP cisplatin can penetrate as far as 4 mm into surface of intraperitoneal tumors (by definition <1 cm in size) and up to six repeated administrations cause an onion skinning effect
 - Administration of 1.5 to 2.0 liters of intravenous normal saline with 40 gm mannitol will assume a renal protective diuresis of unmetabolized cisplatin.
 - Use of an intravenous catheter for IP therapy will help to avoid the development of fibroblast sheath formation that often occurs with intraperitoneal catheters
-

Table 2

Who said all intraperitoneal cisplatin therapy is more toxic than intravenous cisplatin therapy? (17)

[[Toxicity]]	IP Cisplatin (N = 250)	IV Cisplatin (N = 276)	[[p-value]]
Granulocytopenia (%) (grade ≥ 3)	[[56]]	[[69]]	[[0.002]]
Leukopenia (%) (grade ≥ 3)	[[40]]	[[50]]	[[0.04]]
Tinnitus (%) (moderate to severe)	[[7]]	[[14]]	[[0.01]]
Hearing loss (%) (moderate to severe)	[[5]]	[[15]]	[[<0.001]]
Abdominal pain (%) (grade ≥ 2)	[[18]]	[[2]]	[[<0.001]]
Hemoglobin (%) (grade ≥ 3)	[[26]]	[[25]]	[[0.84]]
Thrombocytopenia (%) (grade ≥ 3)	[[9]]	[[8]]	[[0.64]]

Table 3

Dose levels & number of patients

Level (pt #) (total 16)	IP Cisplatin Day 1	[[IP Topotecan]]				
		[[Day 1]]	[[Day 2]]	[[Day 3]]	[[Day 4]]	[[Day 5]]
[[0] (3)] *	[[--]]	[[1.5 mg]]	[[1.5 mg]]	[[1.5 mg]]	[[1.5 mg]]	[[1.5 mg]]
[[1 (4)]]	50 mg/m ²	[[1.5 mg]]	[[1.5 mg]]	[[1.5 mg]]	[[--]]	[[--]]
[[2 (4)]]	50 mg/m ²	[[1.25 mg]]	[[1.25 mg]]	[[1.25 mg]]	[[--]]	[[--]]
[[3 (5)]]	50 mg/m ²	[[1.25 mg]]	[[1.25 mg]]	[[1.25 mg]]	[[1.25 mg]]	[[1.25 mg]]

* one patient with gastric cancer

Table 4

Patient characteristics (excludes 1 patient with gastric cancer)

[[Number entered]]	[[15]]
[[Diagnosis]]	14 epithelial ovarian cancer 1 fallopian tube adenocarcinoma
[[Median age]]	[[49 (range 36–71)]]
[[Performance status]]	[[0–1]]
Positive second look ($\leq$ 1cm residual prior to consolidation therapy)	[[6 (2 microscopic)]]
[[Negative second look]]	[[3]]
[[Metastatic/recurrent disease]]	[[6]]
[[Prior induction]]	Platinum/paclitaxel (12 pts/68 cycles) Cisplatin/capecitabine (1 pt/3 cycles) Carboplatin/cyclophosphamide (1 pt/9 cycles) Cisplatin/topotecan (1 pt/6 cycles)

Table 5

Topotecan pharmacokinetic data

[[Dose level]]	plasma AUC range (ng/ml/hr)	IP AUC range (ng/ml/hr)	[[IP/plasma ratio]]
[[0]]	[[21–32]]	[[2320]]	[[72–110]]
[[1]]	[[21–70]]	[[2507]]	[[35–119]]
[[3]]	[[44–55]]	[[1320–2139]]	[[24–48]]

Table 6

Cross-Trial Comparison of IP Therapy with IV Carboplatin/Paclitaxel

[[Survival]]	[[No Gross Residual]]	[[Negative Second Look]]	[[Progression-Free Survival]]	[[Overall Survival]]	[[2-Year Survival]]	[[4-Year Survival]]
IP Therapy arm of GOG-172 (n=206)	[[38%]]	[[57%]]	[[23.8 mo]]	[[65.6 mo]]	[[83%]]	[[64–65%]]
Carboplatin/Paclitaxel arm of GOG-158 (n=392)	[[35%]]	[[53%]]	[[20.7 mo]]	[[57.4 mo]]	[[83%]]	[[64%]]