2 Management of Ovarian Cancer: Clinical Trials

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Summary

To date, the accomplishment in the area of regional treatment of ovarian cancer has been a major advance in the management of this difficult malignancy. What began as a hypothesis, based on a theoretical mathematical model, has been translated into a 67-mo median survival for women with small-volume residual advanced ovarian cancer *(1)*.

The three major randomized clinical trials on ovarian cancer are detailed in this chapter. The methodology and outcomes, as well as a critique of their design, are presented. Outcomes of these trials to date are described.

Key Words: Intraperitoneal chemotherapy; ovarian cancer; clinical trials.

1. INTRODUCTION

The provocative modeling studies of Dedrick and colleagues at the National Cancer Institute suggested a strong rationale for the intraperitoneal (IP) administration of cytotoxic agents in treatment of advanced ovarian cancer *(1)*. This stimulated other investigators in several centers to explore the clinical implications of this analysis.

Preclinical evaluation, described in some detail in the previous chapter, helped define the patient populations where this strategy had the realistic potential to favorably impact the course of the illness, and pointed out potential concerns (both theoretical and practical) with this approach.

2. PHASE I TRIALS OF THE IP ADMINISTRATION OF CYTOTOXIC ANTINEOPLASTIC AGENTS

Over the past two decades, the use of several antineoplastic and biological agents has been explored in phase 1 clinical trials. The investigation of biologi-

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Table 1
Pharmacokinetic Advantage of Selected Agents with Known Activity in Ovarian Cancer When Administered Directly into the Peritoneal Cavity

Agent	*Ratio: Peritoneal Cavity to Serum*	
	Peak Concentration	**AUC**
Methotrexate *(2,3)*	92	
5-fluorouracil *(4)*	300	360
Melphalan *(5)*	93	65
Doxorubicin *(6)*	470	
Mitoxantrone *(7)*		1,400
Cisplatin *(8–11)*	20	12
Carboplatin *(12,13)*		18
Paclitaxel *(14,15)*	1,000	1,000

AUC, Area-under-the concentration versus time curve

cal agents such as interferon-alpha, interferon-gamma, and interleukin-2 is discussed in Chapter 4.

Table 1 summarizes the pharmacokinetic profile of selected cytotoxic agents with documented anticancer activity in ovarian cancer when delivered directly into the peritoneal cavity *(2–15)*. As predicted by the Dedrick model, the agents demonstrating the greatest difference between cavity and systemic exposures are drugs known to undergo extensive metabolism in the liver (e.g., 5-fluorouracil, doxorubicin, cytarabine, paclitaxel, and mitoxantrone), whereas drugs that do not exhibit this property have a less impressive pharmacokinetic advantage associated with IP administration (e.g., cisplatin and carboplatin). Agents predicted to slowly exit the cavity, based on their unique structural properties (e.g., paclitaxel), also reveal a substantial difference between cavity and systemic exposures after regional delivery.

However, as discussed in the previous chapter, the *relative differences* between local and systemic drug concentrations after IP drug instillation is only one measure of the potential effectiveness of regional treatment. A second important question is the ability of a drug to reach the malignancy by *capillary flow* after regional treatment.

Although it is reasonable to conclude IP administration results in "only a modest" increase in cavity exposure (10–20-fold) compared with the systemic compartment *(8–13)*, for both cisplatin and carboplatin, substantial concentrations of drug instilled into the peritoneal cavity ultimately reach the systemic circulation, such that this route of drug delivery results in essentially equivalent exposure of the tumor to the agent through capillary flow as achieved with intravenous delivery.

The critical point resulting from this analysis is that the IP administration of either cisplatin or carboplatin should, at a minimum, be *equally as effective as systemic therapy* for ovarian cancer, and any effect of the high local concentrations *may add to the benefits* associated with use of this major class of cytotoxic agents.

However, a very different conclusion is reached when analyzing the potential impact of drugs such as paclitaxel, which are limited in the dose that can be delivered into the peritoneal cavity because of their local toxic effects (e.g., abdominal pain), rather than systemic side effects (e.g., bone marrow suppression). Although rather remarkable concentrations of paclitaxel, relative to the systemic compartment, can be achieved (>1,000-fold), very limited concentrations of the active drug are found in the systemic compartment after regional delivery *(14,15)*. Thus, to achieve optimal utilization of this drug in the management of ovarian cancer, it is reasonable to conclude that the agent should be delivered both locally *and* systemically *(16)*.

An additional conclusion from these phase 1 IP trials was the observation that considerable local toxicity could be observed with use of certain drugs (e.g., doxorubicin) *(6,17,18)*. Thus, despite the pharmacokinetic advantage associated with regional delivery, considerable caution would be advised in the administration of these agents. It might be argued that an alternative form of such agents might be developed that could minimize local toxicity (e.g., liposomal preparation) while permitting tumor within the compartment to be exposed to the high concentrations of the agent, possibly with the use of this delivery strategy *(19)*.

During this era, several combination chemotherapy regimens were also explored in phase 1 IP trials, focusing on agents with known activity in ovarian cancer or where theorized synergy between the drugs was possible *(18,20,21)*. There was a particular appeal with this approach, as it permitted the examination of the clinical relevance of highly concentration-dependent interactions noted in preclinical systems.

However, concerns were also raised by this novel strategy. Adding agents together in the fluid volume to be instilled into the peritoneal cavity had the potential to alter the microenvironment (e.g., pH) such that one drug in the combination might become less cytotoxic against the malignant cells, or another agent, with an acceptable local side-effect profile when delivered regionally by itself, might become quite toxic. Finally, it was recognized that if biological activity (e.g., surgically documented tumor regression) was observed in a clinical trial, it would be essentially impossible to know if the responses resulted from one of the individual drugs or actually represented a *synergistic effect* of the combination.

Significantly, the nature of these early phase trials, and the limited populations available, required that investigators carefully select dosing schedules to

be examined. However, alternative strategies might have been chosen that would have been equally valid from the perspective of both toxicity and potential efficacy. Thus, while the platinum agents were principally explored for IP administration on an every 3–4 wk schedule, daily treatment for several days, or a weekly schedule, would have been acceptable options.

3. UNIQUE PHASE I TRIAL EXPERIENCE WITH IP PACLITAXEL

In the case of paclitaxel, compelling data regarding the mechanism of its cytotoxicity (i.e., strongly cycle-specific) argued for a more frequent regional dosing schedule *(22,23)*. Thus, although the initial phase 1 study examining IP paclitaxel in ovarian cancer used the conventional "every 3 wk" treatment strategy *(14)*, a subsequent phase I trial explored its delivery on a weekly schedule *(15)*. Interestingly, use of a lower dose weekly regimen was found to substantially reduce the toxicity (i.e., abdominal pain) associated with IP paclitaxel *(15)*, which had been previously determined to be dose related *(14)*.

The phase I experience with IP paclitaxel also provides a demonstration of the fact that this route can be utilized not only to substantially enhance the *peak levels* of drug in direct contact with tumor but also to profoundly increase the total exposure (area under the curve [AUC]) of a cytotoxic agent to tumor over prolonged periods of time.

In the phase I trial of weekly IP paclitaxel, measurements were made of the concentration of paclitaxel within the peritoneal cavity *immediately preceding* the next weekly dosing schedule (Table 2) *(15)*. The analysis revealed potentially cytotoxic concentrations of the agent persisted for the entire week after treatment. Thus, in theory, the weekly IP delivery of paclitaxel has the potential to permit at least the surface of the cavity, and malignant cells present in this environment, to be *continuously exposed* to the cycle-specific cytotoxic drug *(22,23)*. Further, this provocative goal was accomplished with both an acceptable systemic and local toxicity profile. (Note: The results of a phase 2 second-line ovarian cancer IP paclitaxel trial, conducted by the Gynecologic

Table 2
Concentration of Paclitaxel After IP Delivery*

Administered Dose	*5–7 d After Instillation*
60 mg/m^2	25 µmol/L
65 mg/m^2	35 µmol/L
65 mg/m^2	20 µmol/L

*Individual patients treated at specified dose levels *(15)*.

Oncology Group based on this observation, will be discussed later in this chapter) *(24)*.

4. IMPACT OF CHANGING CONCEPTS OF OVARIAN CANCER TREATMENT ON IP DRUG DELIVERY STRATEGIES

These phase I studies were conducted over a period of two decades, which partially explains modifications in the concepts of optimizing treatment programs in the IP arena. As data from accumulating clinical trials more clearly defined both the relevance of "dose intensity" and methods to reduce the toxicity of specific agents, these ideas were employed by investigators exploring regional drug delivery strategies. For example, the initial trials of IP carboplatin determined IP dosing based on "mg/m^2" *(12,13)*, whereas later studies used AUC dosing strategies *(25)*.

Further, early phase I (and some phase II) trials of IP cisplatin explored the potential of substantially increasing the administered dose using this route of delivery *(8,18,20,21)*. During this era of drug development in oncology, there was a fundamental belief that "more is better" when delivering cytotoxic agents, and this general treatment philosophy played a major role in many chemotherapeutic approaches in ovarian cancer (and other malignancies).

However, a series of highly *negative* prospective phase III randomized trials in the treatment of ovarian cancer have convincingly demonstrated that this concept is seriously flawed, at least at the concentrations of currently available cytotoxic agents that can be *safely attained* within the *systemic compartment* after intravenous drug delivery *(26–29)*. These trials revealed that by "doubling" the dose intensity of systemically delivered platinum (e.g., cisplatin from 50 mg/m^2 to 100 mg/m^2 and carboplatin from AUC 6 to AUC 12), toxicity substantially increased without any change in survival.

It is critical to emphasize that this negative experience with dose intensity in randomized phase III trials in ovarian cancer relates to what can currently be achieved with *systemic drug delivery*, and does not suggest that the fundamental concept is actually wrong. On the contrary, it is conceivable that at the far higher local drug concentrations achievable locally after IP drug delivery (e.g., 10–20-fold for cisplatin and carboplatin *(8–13)* and >1,000-fold for paclitaxel *(14,15)*), a clinically relevant impact of "dose–response" might be observed.

Thus, conceptually, *maximizing the amount of platinum* achieved within the systemic compartment with IP administration should currently be understood to *not be a goal of regional drug delivery*. Rather, the aim should be to attain a systemic drug concentration that permits sufficient delivery of the platinum agent to the tumor by *capillary flow*, as previously defined in phase III randomized clinical trials *(26–29)*.

5. EVALUATION OF THE BIOLOGICAL ACTIVITY OF IP CYTOTOXIC CHEMOTHERAPY IN THE MANAGEMENT OF OVARIAN CANCER

After the completion of phase I studies, which defined the pharmacokinetic properties and safety of both single-agent and several combination chemotherapy IP programs, investigators in several centers and cooperative groups initiated a series of platinum-based phase II IP efficacy trials in patients with ovarian cancer *(24,30–40)*.

Before briefly reviewing and summarizing the results of these studies, it is important to discuss the method by which "efficacy" was defined. In most *traditional* phase II oncology trials, patients with "measurable" mass lesions, based on physical exam findings or (more commonly) radiographic evaluation, are treated with a particular experimental program, and response is determined based on a prospectively defined percentage of shrinkage of those tumor nodules/masses.

However, although such an approach could have been used to evaluate the effectiveness of an IP regimen in a phase II trial, a decision to perform this type of analysis would have been a serious error. As previously noted, the setting where the benefits of an IP treatment program might be rationally anticipated would be in patients with either documented microscopic IP cancer, or where only very small-volume macroscopic disease was present (<0.5-cm–1-cm tumor masses) when the regional strategy was initiated *(41–43)*. Conversely, extensive preclinical evaluation (discussed in the preceding chapter) had strongly suggested there would be minimal (or no) activity observed after IP therapy of larger macroscopic tumor masses.

Treatment of patients with tumor nodules that could be imaged by a CT scan of the abdomen/pelvis would likely require IP disease of at least 2 cm in diameter, which is far larger than what existing data would suggest is appropriate for successful use of this route of drug delivery. Given this information, how can the biological activity of IP therapy be evaluated? Fortunately, in the management of patients with ovarian cancer, there is long-established and accepted experience, with surgical reassessment after the completion of primary chemotherapy programs ("second-look laparotomy") *(44,45)*.

Thus, in several centers exploring the activity of IP therapy in women with ovarian cancer, patients who had "relatively small-volume disease" at the time of performance of a second-look surgical procedure were treated on an Institutional Review Board (IRB)-approved phase 2 IP chemotherapy trial, and, subsequently, underwent a "third-look" surgery (laparotomy or, more recently, laparoscopy) to evaluate the reduction in tumor volume (compared to what was observed before treatment) or the absence of any histologic evidence of persistent cancer ("negative third-look").

6. PHASE II TRIAL EXPERIENCE WITH IP CISPLATIN IN OVARIAN CANCER

Predictably, based on its central role in the management of ovarian cancer, much of the initial phase II trial effort (both single-agent and combination chemotherapy regimens) in the malignancy focused on cisplatin *(30–37)*.

Further, with few exceptions, the early phase II IP trials in ovarian cancer were directed toward treating women with this strategy as a "second-line" treatment approach. Exploration of the activity of IP cisplatin in this particular clinical setting permitted a most interesting, and rather unique, analysis.

Because essentially all patients entered into the phase II, second-line, IP cisplatin–based trials had received the same agent (or the equivalent drug, carboplatin) delivered intravenously as a component of primary chemotherapy, the activity of *IP cisplatin* could be indirectly compared to the activity of *systemically delivered cisplatin* (or carboplatin). In addition, because the IP delivery followed documentation of the extent of response to the intravenous treatment program, it was reasonable to speculate that any "observed biological activity" of the second-line approach was related to the specific *route of delivery*, rather than only the effect of cisplatin itself, because the "cisplatin effect" would have been seen with the intravenous regimen *(46)*.

It is essential to note that any such comparisons (to be described later in this chapter) are merely "*hypothesis generating*," or supportive of further clinical investigation. In the absence of data from prospective randomized phase III trials examining the impact of treatment on survival, it is completely unknown if the observation of "additional tumor cell kill" actually benefits patients.

As rather accurately predicted by the preclinical studies, substantially more "biological activity" (surgically defined tumor shrinkage, conversion of "positive" second-look laparotomies to "negative" third-look procedures) was observed for second-line IP cisplatin in patients with small-volume disease, compared with those individuals with larger tumor masses *(47)*. This point is emphasized by the extensive published experience of the Gynecologic Cancer program of the Memorial Sloan-Kettering Cancer Center with second-line, cisplatin-based IP chemotherapy in ovarian cancer (Table 3) *(47)*.

In addition, and not necessarily predicted by the previously conducted preclinical evaluations, the accumulating data in this area revealed another highly relevant limitation of IP cisplatin. The Memorial Sloan-Kettering group demonstrated impressive surgically defined biological activity for IP cisplatin in patients with ovarian cancer whose malignancy had previously responded to intravenous cisplatin, but who persisted in having "small-volume residual disease" at the time of a second-look laparotomy *(47)*. However, the group also showed that there was essentially no activity observed with this regional strategy in patients with similarly defined small-volume disease, except where the

Table 3
Surgically Documented Complete Response Rate to Second-Line Cisplatin-Based IP Chemotherapy of Ovarian Cancer *(47)*

	Largest Residual Tumor Mass	
	Microscopic	**>1 cm**
Prior response to intravenous cisplatin	6/13 (46%)	2/16 (13%)
No prior response to intravenous cisplatin	1/4 (25%)	0/23 (0%)

cancer had actually failed to exhibit evidence of a response to the primary cisplatin-based intravenous chemotherapy program.

Thus, these data provide strong support for the concept that the high concentrations of platinum achievable within the peritoneal cavity (10–20-fold greater than present within the systemic circulation) are able to overcome a *modest level of resistance* to the agent, in that additional cell kill is observed when disease is found to persist in the setting of documentation of a *response* to the intravenous treatment. In sharp contrast, where the tumor has shown itself to possess an inherent *major level of resistance*, the concentration of platinum present within the peritoneal cavity after regional drug delivery is unable to produce a biologically relevant effect. Notably, these data are quite consistent with the previously published experience with high dose intravenous chemotherapy and autologous bone marrow transplantation used in the management of ovarian cancer *(48)*.

Several phase II single-agent cisplatin– and combination cisplatin–based IP chemotherapy trials have been reported, with similar levels of observable surgically documented biological activity *(30–37)*. The results of these studies do not suggest the superiority of any particular cisplatin-based regional treatment strategy, including the use of "high dose" IP cisplatin (combined with sodium thiosulfate rescue) *(8,36)*.

Again, in the *second-line setting*, what the data make quite clear is that patients with ovarian cancers that are inherently resistant to platinum (documented by failure to respond to primary chemotherapy), or those with larger volume disease (maximum tumor mass >1 cm in maximum diameter) are highly unlikely to benefit from this therapeutic strategy *(47)*. Conversely, for those individuals whose cancers have responded to initial chemotherapy, but microscopic or small-volume macroscopic disease (<0.5 cm maximum diameter) persists, a substantial percentage of such patients (30–40%) may be anticipated to attain the state of "surgically documented complete response" (if this surgery were performed) after treatment with an IP cisplatin–based regimen.

Unfortunately, evidence of a *biological effect* (e.g., objective tumor shrinkage or conversion of a "microscopically positive" second-look surgery to "micro-

scopically negative third-look surgery") does not necessarily signify that patients have experienced *clinical benefit* (e.g., improved symptoms or progression-free and overall survival) from the strategy. Only appropriately designed prospective randomized phase III trials can definitively address this question.

However, it is interesting to note that several groups have reported an impressive experience with long-term (>4–5 yr) survival for ovarian cancer patients treated with *second-line* cisplatin-based IP chemotherapy *(49–52)*. Whether this favorable outcome reflects the benefits of this management approach, the natural history of disease in a subset of patients with favorable biological characteristics (e.g., initial response to chemotherapy with minimal disease at second-look surgery), or a combination of these two factors remains unknown in the absence of data from a phase III trial.

A final cisplatin-based IP phase II trial experience is worthy of particular mention. Investigators at the Memorial Sloan-Kettering Cancer Center treated a group of ovarian cancer patients who were found to be without histologic evidence of disease at the time of performance of a second-look laparotomy with three cycles of IP cisplatin and etoposide *(53)*. The researchers subsequently compared the risk of documented disease relapse in this population to a contemporaneous "historical control" group at their institution that was in an identical clinical state, and would have been eligible for entry into this phase II trial, but for various reasons (e.g., patient/physician choice) *did not* receive this consolidation strategy. Interestingly, the investigators found that the rate of ultimate relapse was greater (54% vs 39%) in the historical control group *(53)*.

Although it is appropriate to conclude that such published retrospective comparisons to historical controls should generally be ignored, as the most likely explanation for the finding is that the nonrandomized "experimental study arm" population simply had more favorable "baseline clinical characteristics" that could account for this "apparent favorable outcome," the exact opposite was the case in this analysis. In fact, the historical control group, which was found to have the greater risk of relapse, possessed the more favorable baseline features, including having a higher percentage of individuals who were stage II (39% vs 8%), and a lower percentage of individuals with suboptimal disease (20% vs 33%) when primary chemotherapy was initiated.

Again, although not a randomized trial, these data are quite provocative, and suggest another setting where IP cisplatin–based chemotherapy may be rationally employed.

7. NON–CISPLATIN-CONTAINING PHASE II IP CHEMOTHERAPY TRIALS

IP carboplatin has been examined as a single agent, and in several combination chemotherapy programs, with surgically documented activity observed in the settings of both primary and second-line treatment of ovarian cancer *(38–*

40). Overall, the objective response rates are comparable to that seen with IP cisplatin in similar patient populations. However, some concern has been expressed for a potentially lower response rate to carboplatin in the presence of *macroscopic* residual disease, compared to the older platinum drug, when the agents are employed as second-line therapy *(54)*.

The experience with IP paclitaxel is of particular interest. In a Gynecologic Oncology Group phase II trial, paclitaxel was administered on a weekly schedule (60 mg/m^2) for 16 wk *(24)*. Of the 28 patients who initiated regional treatment with *microscopic disease only* (documented at the prior performance of a second-look laparotomy), 17 (61%) attained a surgically documented complete response, in contrast to only 1 in 31 patients (3%) who achieved this state if they started second-line IP paclitaxel with any evidence of *macroscopic cancer*.

These data reinforce the importance of tumor volume in influencing the activity of IP therapy, particularly when relying almost exclusively on direct uptake of the agent from the cavity into the malignant cell population, when there is limited (or no) delivery of the drug through the vascular compartment. Further, this experience emphasizes the relevance of a "combined intravenous/IP" approach when employing paclitaxel, or a cytotoxic drug with similar biological properties *(16)*.

Other single agents explored in phase II IP trials in ovarian cancer included cytarabine *(55)*, mitoxantrone *(56,57)*, 5-fluorouracil *(58)*, and fluoroxidine *(57)*.

8. PHASE III TRIAL OF IP VERSUS INTRAVENOUS CISPLATIN (WITH ALL PATIENTS ALSO RECEIVING INTRAVENOUS CYCLOPHOSPHAMIDE) AS PRIMARY TREATMENT OF SMALL-VOLUME RESIDUAL ADVANCED OVARIAN CANCER

The aforementioned experience with second-line cisplatin-based IP chemotherapy led the Southwest Oncology Group and the Gynecologic Oncology Group to initiate a randomized phase III trial directly, comparing a regimen of IP cisplatin to intravenous cisplatin as primary treatment of small-volume residual advanced ovarian cancer, after an attempt at optimal surgical cytoreduction (Table 4) *(59)*. All patients also received intravenous cyclophosphamide as the second drug in the combination program.

In this trial, small-volume residual disease was defined as the largest remaining tumor nodule, being <2 cm in maximal diameter. The study was well balanced for known prognostic factors in the malignancy.

The trial found that patients treated with the IP cisplatin program experienced a lower incidence of neutropenia, tinnitus, and hearing loss (presumably caused by reduced peak levels of platinum within the vascular compartment and marginally lower total systemic exposure to the agent), but a greater risk of abdomi-

Table 4
Randomized Phase III Trials of IP Versus Intravenous Cisplatin-Based Primary Chemotherapy of Small-Volume Residual Advanced Ovarian Cancer

Study	*Progression-Free Survival (Median in Months)*	*Overall Survival (Median in Months)*	*Control Arm*	*Experimental Arm*
Study 1 *(59)*	–	48 vs 41 ($p = 0.02$) HR 0.76	cisplatin 100 mg/m^2 IV plus cyclophosphamide 600 mg/m^2 IV q 21-d × 6	cisplatin 100 mg/m^2 IP plus cyclophosphamide 600 mg/m^2 IV q 21-d × 6
Study 2 *(62)*	28 vs 22 ($p = 0.02$) HR 0.78	63 vs 52 ($p = 0.05$) HR 0.81	paclitaxel 135 mg/m^2 IV over 24-hours plus cisplatin 75 mg/m^2 IV q 21-d × 6	carboplatin AUC 9 IV q 28-days × 2; followed by Paclitaxel 135 mg/m^2 IV over 24-hours cisplatin 100 mg/m^2 IP (day 2) q 21-d × 6
Study 3 *(16)*	24 vs 18 ($p = 0.05$) HR 0.79	66 vs 50 ($p = 0.03$) HR 0.71	paclitaxel 135 mg/m^2 IV over 24 hours plus cisplatin 75 mg/m^2 IV q 21-d × 6	paclitaxel 135 mg/m^2 IV over 24 hours plus cisplatin 100 mg/m^2 IP (day 2) plus Paclitaxel 60 m/mg^2 IP (day 8) q 21-d × 6

nal pain (principally, mild to moderate in severity). There was no difference in treatment-related mortality between the two treatment arms.

Of considerable importance, patients randomized to receive IP cisplatin experienced superior overall survival compared with systemic delivery of the agent (median: 49 mo vs 41 mo; $p = 0.02$) *(59)*.

9. PHASE III TRIAL OF IP VERSUS INTRAVENOUS CISPLATIN (WITH ALL PATIENTS ALSO RECEIVING INTRAVENOUS PACLITAXEL) AS PRIMARY TREATMENT OF SMALL-VOLUME RESIDUAL ADVANCED OVARIAN CANCER

Despite the impressive impact of IP treatment found in the initial phase III trial, many investigators questioned whether the benefits associated with regional cisplatin drug delivery could be achieved by simply substituting paclitaxel for cyclophosphamide, based on the finding at that time of the superiority of the taxane-containing regimen when used in advanced ovarian cancer *(60,61)*.

Thus, a second phase III trial was initiated by the Gynecologic Oncology Group, the Southwest Oncology Group, and the Eastern Cooperative Oncology Group, which directly compared the "new" systemically administered "gold standard" regimen of intravenous cisplatin plus paclitaxel to an experimental program of intravenous paclitaxel plus IP cisplatin (Table 4) *(62)*. Of note, in this study, small-volume residual advanced ovarian cancer was defined as the largest tumor mass, being <1 cm in maximum diameter.

This trial added a second novel component to the experimental regimen. In an effort to employ the regional therapy in a setting where the "smallest possible tumor volume" was present when IP treatment was initiated (as predicted by the previously described preclinical models and limited clinical experience *(47,63)* to be a rational strategy), patients randomized to this study arm were given two cycles of "moderately high dose" intravenous carboplatin (AUC 9) to *chemically debulk* the tumor before receiving IP cisplatin *(62)*.

Although theoretically a reasonable approach, the initial intravenous carboplatin resulted in an unanticipated incidence of severe and persistent bone marrow suppression (principally thrombocytopenia), such that approximately 20% of the patients randomized to the experimental arm ultimately received up to two courses of IP cisplatin *(62)*. Although not a direct result of the regional treatment, patients experiencing prolonged cytopenias were required to be removed from the investigative program.

Despite this, women randomized to the experimental study arm experienced a statistically significant improvement in both progression-free (28 mo vs 22 mo; $p = 0.02$) and overall survival (63 mo vs 52 mo; $p = 0.05$) *(62)*. Thus, even though *all patients* entered into this study received intravenous paclitaxel, the

use of IP cisplatin *further extended survival*. In this regard, it is interesting to note that this trial was the first randomized study in advanced ovarian cancer to achieve a median overall survival of >5 yr in one of the study arms (IP cisplatin).

It is also important to comment here on a possible specific role for the two courses of "moderately high dose" carboplatin in the observed survival benefits in this trial. As previously mentioned, several randomized phase III trials examining a role for *dose intensity* in the range of the carboplatin dose used in this study have failed to demonstrate any benefit in favorably impacting survival *(26–29)*. Thus, it is highly unlikely that the two courses of carboplatin used before the administration of IP cisplatin had a direct influence on the trial's outcome.

10. PHASE III TRIAL OF INTRAVENOUS CISPLATIN/ PACLITAXEL VERSUS IP CISPLATIN PLUS BOTH IP AND INTRAVENOUS PACLITAXEL

The most recent randomized phase III trial, which was conducted by the Gynecologic Oncology Group, directly compared a regimen of intravenous cisplatin plus paclitaxel (control arm) to an "experimental program" consisting of IP cisplatin plus both IP *and* intravenous paclitaxel as primary chemotherapy of small-volume residual advanced ovarian cancer (Table 4) *(16)*. (The rationale for combining intravenous and IP paclitaxel is discussed earlier in this chapter, as well as in the preceding chapter.)

In an effort to avoid direct interactions between cisplatin and paclitaxel within the instilled treatment volume (and the unknown consequences of such an event), the regionally delivered paclitaxel was administered on day 8 of each 21-d treatment cycle. The largest volume of residual disease permitted for entry into this trial was, again, <1 cm in maximum diameter.

Patients treated on the experimental arm of this phase III trial experienced a higher incidence of several systemic toxicities (e.g., emesis, bone marrow suppression, and neuropathy) and more abdominal discomfort. However, of considerable importance, a *formal quality-of-life analysis* was performed as a prospective component of this trial; although there was a lower measured quality-of-life associated with the IP regimen *during the treatment program*, at the 12-mo follow-up there was no difference between the regimens *(16)*.

Of greatest significance, this study once again revealed that treatment with a cisplatin-based IP program resulted in a highly statistically significant improvement in both progression-free survival (24 mo vs 18 mo; $p = 0.05$) and overall survival (66 mo vs 50 mo; $p = 0.03$), and was the *third randomized phase III trial to reach this conclusion*.

11. IMPLICATIONS OF THE CURRENT IP CHEMOTHERAPY DATA FOR THE PRIMARY CHEMOTHERAPEUTIC MANAGEMENT OF SMALL-VOLUME RESIDUAL ADVANCED OVARIAN CANCER

The data from these three randomized phase III trials have now firmly established a new *standard of care* in the primary chemotherapeutic management of small-volume residual advanced ovarian cancer *(16,59,62)*. Collectively, they indicate that patients treated with cisplatin by the IP route experience a 20%–30% reduction in the risk of death compared with intravenous drug delivery.

These results are similar to those previously documented when paclitaxel was substituted for cyclophosphamide in the management of ovarian cancer *(60,61)*. Of great importance, it is now clear the use of IP cisplatin *adds* to the benefits attained by using intravenous paclitaxel.

However, as is very often the case in oncology, the results of these three landmark trials do raise several highly clinically relevant questions: Is it necessary to employ IP cisplatin at a dose of 100 mg/m^2, or can a somewhat lower dose be utilized to reduce the toxicity of treatment? Can IP carboplatin be substituted for cisplatin? What is the role of IP paclitaxel?

Although definitive answers to these (and other) questions are currently not available, the following are reasonable responses, based on existing data, which may be utilized by oncologists considering IP chemotherapy in this clinical setting.

First, while it is quite appropriate to employ an IP cisplatin dose of 100 mg/m^2, based on the findings of the three randomized phase III trials *(16,59,62)*, it is also rational to argue that moderately lowering the cisplatin dose (75–80 mg/m^2) will *not* reduce the efficacy of treatment (continued high local concentrations, minimal decrease in systemic exposure) *(26–29)*. Further, for many patients, a modest dose reduction may make it possible for the cisplatin-based treatment to be far better tolerated (e.g., reduced emesis and neuropathy).

Second, although IP carboplatin has been successfully employed in the phase II setting *(25)*, including in combination with intravenous paclitaxel, all randomized trials (to date) that have shown a *major survival advantage* have utilized IP cisplatin. Thus, it would be reasonable to conclude that unless a particular patient experiences unacceptable systemic toxicity from cisplatin, or simply refuses to receive the agent, the initial regional treatment program should utilize cisplatin. In the setting of significant cisplatin-related toxicity (e.g., emesis), substitution with IP carboplatin is a highly rational management option *(25)*.

Finally, although IP paclitaxel was utilized in the third randomized trial (showing the greatest impact on survival) *(16)*, the previous two studies that also revealed a favorable effect on overall survival did not employ this agent administered regionally *(59,62)*. Further, it is quite possible that much of the

abdominal pain observed in the most recent trial may have been caused by the paclitaxel *(14,15)*.

Thus, one rational option for management may be to begin the IP treatment program with only the cisplatin delivered regionally. If the initial cycle is tolerated reasonably well, in regard to the development of abdominal discomfort, IP paclitaxel can be added to the second (and future) cycles. However, if even "modest" abdominal pain is noted with IP cisplatin alone, it may be prudent to avoid the addition of regional paclitaxel that may significantly worsen the local discomfort and, in fact, prevent the completion of the planned IP treatment program.

12. FUTURE DIRECTIONS IN THE USE OF IP CHEMOTHERAPY IN THE MANAGEMENT OF OVARIAN CANCER

The results of three large prospective randomized phase III trials have now established IP chemotherapy as the standard of care in the primary chemotherapeutic management of small-volume residual advanced ovarian cancer *(16,59,62)*. Much research remains to be done in this arena, including focusing major efforts to improve methods of drug delivery (discussed in Chapter 5), exploring novel antineoplastic agents administered regionally, and developing innovative strategies to enhance drug penetration and distribution.

Further, based on currently available data and knowledge of the natural history of the course of this disease, it is reasonable to propose the conduct of prospective randomized phase III trials in other settings involving patients with ovarian cancer (Table 5).

In conclusion, what has been accomplished to date in the area of regional treatment of ovarian cancer has been a major advance in the management of this difficult malignancy. What began as a hypothesis based on a theoretical

Table 5
Additional Potential Indications for IP Chemotherapy in the Management of Ovarian Cancer

1. *Primary treatment* of "early-stage" high-risk ovarian cancer (stage IC, stage 2)
2. *Consolidation treatment* following attainment of a surgically defined complete response *(53)*.
3. "*Second-line treatment*" with microscopic/minimal macroscopic residual cancer confirmed at a reassessment surgery in a patient with documented response to primary platinum-based systemic chemotherapy
4. Treatment following a major surgically confirmed response (minimal residual disease) to neoadjuvant chemotherapy.

mathematical model *(1)* has been translated into a 67-mo median survival for women with small-volume residual advanced ovarian cancer. Yet, we are truly only at the "end of the beginning."

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