Intraperitoneal chemotherapy in the management of ovarian cancer: focus on carboplatin

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Abstract: Both pre-clinical studies and phase 1–2 clinical trials have provided strong support for the potential role of regional drug delivery in the management of epithelial ovarian cancer, a disease process whose major manifestations remain largely localized to the peritoneal cavity in the majority of individuals with this malignancy. The results of 3 phase 3 randomized trials have revealed the favorable impact of primary cisplatin-based intraperitoneal chemotherapy in women who initiate drug treatment with small-volume residual ovarian cancer following an attempt at optimal surgical cytoreduction. Concerns have been raised regarding the toxicity of regional treatment, particularly the side-effect profile associated with cisplatin. One rational approach to improving the tolerability of intraperitoneal chemotherapy is to substitute carboplatin for cisplatin. This review discusses the rationale for and data supporting regional treatment of epithelial ovarian cancer, and highlights the potential role for intraperitoneal carboplatin in this clinical setting.

Keywords: ovarian cancer, intraperitoneal chemotherapy, cisplatin, carboplatin

Due to its location in the peritoneal cavity,[1,2] many have considered direct intraperitoneal delivery of anti-neoplastic agents a rational approach to the management of ovarian cancer. In fact, reports in the early days of the development of cytotoxic chemotherapeutic agents revealed the potential for this strategy to improve symptoms in this malignancy, particularly those associated with the accumulation of malignant ascites.[3,4]

Unfortunately, those initial experiences essentially failed to demonstrate superior efficacy associated with regional drug administration, compared to systemic (intravenous or oral) delivery, and the additional time and effort required made this a rather unattractive management option. Further, for certain drugs (eg, cytotoxic alkylating agents with vesicant properties), substantial local toxicity (eg, abdominal pain, adhesion formation leading to bowel obstruction) could be added to the known existing side effects of a particular drug (eg, emesis, bone marrow suppression).[5,6]

"Dedrick model" of regional treatment of ovarian cancer

In the late 1970s, Robert Dedrick and his colleagues at the National Cancer Institute (Bethesda, MD, USA), published a landmark theoretical modeling study which predicted that for anti-neoplastic agents possessing particular biological properties there would be a major pharmacokinetic advantage for exposure of the drug to cancer present within the peritoneal cavity following regional delivery, compared to systemic administration of the same agent.[7] These provocative data and subsequently conducted pre-clinical evaluations provided a strong impetus for clinical investigators to renew their interest in exploring the concept of intraperitoneal treatment in the management of ovarian cancer.

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Rational selection of anti-neoplastic agents for intraperitoneal chemotherapy

Based on both the preclinical experience and the results of early phase clinical trials a number of features can be identified that would predict a particular anti-neoplastic drug might exhibit favorable properties if utilized via the intraperitoneal route.

First, it is critical that the agent is not a vesicant or major irritant, as it has been clearly noted the resulting inflammation can cause considerable local pain and subsequent adhesion formation.[5] This event may interfere with drug distribution throughout the cavity, negatively influencing the efficacy of regional treatment. Further, in addition to the acute reversible effects, more serious toxicity can develop (eg, bowel obstruction leading to required surgical intervention).

Second, agents that are slowly removed from the peritoneal cavity and rapidly cleared from the systemic circulation will exhibit the greatest pharmacokinetic advantage following regional delivery. In this regard, drugs that are rapidly and extensively metabolized into non-toxic metabolites during their first-pass through the liver are particularly attractive for intraperitoneal administration, as it has long been recognized that drug uptake from the cavity is largely via the portal circulation.[8,9]

Third, preclinical data demonstrating that an agent is biologically active against the particular malignancy (eg, ovarian cancer), and that the activity can be substantially enhanced when the malignant cells are exposed to higher peak concentrations of drug, or for considerably longer periods of time (greater area-under-the concentration-versus-time curve [AUC]), than can safely be achieved following systemic delivery, provides a strong rationale for examining regional administration in the clinical setting.[10]

Phase 1 trials of intraperitoneal therapy in ovarian cancer

Over the last several decades, a rather large number of anti-neoplastic drugs have been examined for their safety and pharmacokinetic properties when delivered by the intraperitoneal route (Table 1).[11] Importantly, the relative limited local toxicity associated with certain agents (including cisplatin and carboplatin) was confirmed in these studies.[11,12–18] although this critically relevant finding was not universal (eg, pain associated with intraperitoneal doxorubicin).[19]

As predicted by the "Dedrick Model", those drugs known to undergo extensive metabolism during their first pass

Table 1 Pharmacokinetic advantage associated with intraperitoneal delivery of anti-neoplastic agents with known activity in ovarian cancer

Ratio: peak levels peritoneal cavity to systemic circulation	
Cisplatin	20
Carboplatin	18
Paclitaxel	1000
Doxorubicin	470
Melphalan	80
5-fluorouracil	300

through the liver have been shown to possess the greatest pharmacokinetic advantage following intraperitoneal administration.[11] However, data for agents with more modest differences between total or peak exposures of the peritoneal and systemic compartments to the biologically active anti-neoplastic agents (eg, 10- to 20-fold for cisplatin, carboplatin) are of considerable interest and potential clinical relevance because these concentrations are simply not realistically attainable within the systemic compartment due to production of severe side effects (eg, bone marrow suppression; renal toxicity and neurotoxicity).

Further, provocative pre-clinical data for the platinum agents had revealed that resistance to these drugs can actually be quite "relative", and may conceivably be overcome by exposing tumor cells to only modestly higher (eg, 2- to 4-fold) concentrations of the drugs compared to that documented to be within the systemic compartment following standard systemic treatment.[20] Unfortunately, extensive prior clinical experience has revealed that even "doubling the dose" and concentration of cisplatin (eg, 75 mg/m^2 to 150 mg/m^2) or carboplatin (AUC 6 to AUC 12), and administering multiple cycles of such a regimen, would unquestionably lead to unacceptable toxicity. However, these higher concentrations, as well as the increased peak levels and AUCs are theoretically rather easily achievable within the confines of the peritoneal cavity following regional administration of the platinum drugs.

Depth of drug penetration: the major limiting factor associated with regional chemotherapy

The early phase 1 clinical trials provided a strong rationale for further exploration of regional treatment of ovarian cancer. However, extensive pre-clinical experience suggested that despite the impressive pharmacokinetic advantage associated with regional therapy this management approach would find

its greatest utility in the setting of small volume residual macroscopic cancer or microscopic disease only, due to the very limited ability of such drugs to penetrate into solid tissue.[21–24]

Such penetration was observed in several modeling systems to range from a few cell layers to 1 to 2 mm from the cell surface. Of note, in a series of studies specifically examining the penetration of cisplatin in a rat model, the relative advantage of exposure to platinum, associated with intraperitoneal compared to systemic delivery, was a maximum of approximately a millimeter from the cell surface.[22]

These data would indicate that patients with large volume residual ovarian cancer would be unlikely to benefit from intraperitoneal delivery because the high concentrations of drugs measured within the cavity itself would not reach very deep into any residual tumor. However, one might also speculate that if a malignant mass lesion was substantially reduced in volume by exposure to biologically active systemic therapy regional drug delivery may be effective in subsequent courses against the smaller residual disease.[25]

Further, since it is known that platinum (both cisplatin and carboplatin) reaches the systemic compartment in essentially full concentrations following regional administration (largely due to the fact there is very limited metabolism of the agents within the liver), it is not unreasonable to consider the administration of a platinum drug intraperitoneally even in the setting of larger volume cancer.[12–18] This conclusion follows from the hypothesis that there will be satisfactory concentrations of the drug reaching tumor by capillary flow, and with subsequent courses the smaller volume residual tumor may benefit from substantially greater local exposure associated with the intraperitoneal drug instillation. Of course, this is a hypothesis that is testable in a randomized phase 3 clinical trial.

Phase 2 trial experience with intraperitoneal chemotherapy of ovarian cancer

Not surprisingly, due it its established role in the management of ovarian cancer, the majority of experience examining regional delivery of anti-neoplastic drug therapy in ovarian cancer has focused on the platinum agents, principally cisplatin.[11,26] Further, most of the trials have been in the second-line setting, following primary platinum-based systemic chemotherapy.

These circumstances permit an interesting perspective, in that is it possible to inquire about the level of biological activity observed with regional platinum delivery, compared

to that of an individual patient's prior experience with intravenous platinum. One published study specifically examined this question and noted that tumors that had not previously exhibited tumor regression to the concentrations of platinum attainable with systemic therapy rarely responded to regional treatment (with activity documented at surgical reassessment).[26] This was the case even if the patient had only very small volume residual cancer when the second-line cisplatin-based intraperitoneal treatment program was initiated.

Conversely, in patients whose cancers had achieved partial responses to prior platinum therapy, as many as 30% to 40% of such individuals were found to have attained a surgically documented complete response to intraperitoneal cisplatin. Of interest, these provocative data support the general concept that the high concentrations of platinum noted following regional treatment are able to overcome a modest level of existing resistance. However, unfortunately, the attainable concentrations are unable to influence major inherent platinum resistance.

Intraperitoneal carboplatin was also examined in several phase 2 trials in women with ovarian cancer in the second-line setting.[14,27–30] In fact, overall, the drug demonstrated measurable biological activity quite comparable to that seen with cisplatin. This observation is not surprising in view of the known equivalence of the two platinum agents in advanced ovarian cancer when delivered systemically at optimal doses.

One retrospective analysis examining a single institutional experience employing either intraperitoneal cisplatin or carboplatin-based chemotherapy in the second-line setting noted similar surgically defined objective response rates to the two strategies in individuals who initiated chemotherapy with microscopic residual disease.[31] However, a lower response rate was observed with carboplatin in women with any residual macroscopic cancer when the regional treatment program was initiated.

This clinical experience was similar to one reported pre-clinical evaluation that suggested the amount of measurable platinum within macroscopic tumors was lower with carboplatin than cisplatin following regional administration,[32] but it is important to note these data have not been confirmed in any other pre-clinical model, or clinical experience with the two platinum strategies. Further, there have been no phase 3 randomized trials in the second-line setting to confirm (or refute) the utility of regional drug delivery with either cisplatin or carboplatin (or any other agent) in this patient population.

Intraperitoneal carboplatin has also been examined in the phase 2 setting as a component of primary chemotherapy of advanced ovarian cancer.[14,33,34] These non-randomized studies demonstrate the feasibility of the approach, and interesting survival data have been reported. What is missing are phase 3 trial data employing the agent in this manner.

Phase 3 trials of cisplatin-based primary chemotherapy of small volume residual advanced ovarian cancer

Several phase 3 randomized trials have now been reported that explored the clinical utility of regional cisplatin chemotherapy employed as primary chemotherapy of small volume residual advanced ovarian cancer following an attempt at maximal cytoreductive surgery.[35–37] Three of these studies were of sufficient sample size and design to potentially provide definitive answers to the question of the utility of regional cisplatin in this setting (Table 2).

The first trial, conducted by the Southwest Oncology Group (SWOG) and the Gynecologic Oncology Group (GOG) compared the same dose (100 mg/m^2) of either intraperitoneal or intravenous cisplatin.[35] All patients entered into this study also received intravenous cyclophosphamide. The largest residual tumor mass size permitted entry into this trial was 20 mm. Patients randomized to the intraperitoneal study arm experienced more abdominal discomfort (generally mild to moderate in severity), but no increase in severe clinical toxicity or treatment-related deaths. Further, there was a reduced incidence of neutropenia and tinnitus associated with local drug delivery. Of greatest importance, the study revealed a statistically significant improvement in overall survival associated with regional delivery of cisplatin in this clinical setting (Table 2).

A second primary ovarian cancer regional chemotherapy trial was then conducted by the GOG and SWOG, with the addition of the Eastern Cooperative Oncology Group (ECOG) which again compared intraperitoneal cisplatin to intravenous cisplatin, but in this study all patients also received intravenous paclitaxel, rather than intravenous cyclophosphamide.[36] Of note, the largest size of a residual mass lesion permitted entry into this trial was 10 mm.

This study added another novel component, based on the previously stated belief that regional drug delivery would be most relevant in those patients with the smallest residual tumor volumes. Thus, prior to the administration of regional chemotherapy, patients randomized to this study arm received 2 cycles of "moderately high dose" intravenous carboplatin (AUC 9) designed to "chemically debulk" any residual macroscopic cancer remaining after the initial cytoreductive surgery.[38]

Unfortunately, the two courses of intravenous carboplatin produced an unexpectedly high incidence of severe thrombocytopenia, such that 19% of patients received two or fewer courses of intraperitoneal drug delivery. This outcome was a direct result of carboplatin-associated bone marrow suppression and not local toxic effects of the regional treatment program. Despite this fact, this study revealed improved progression-free survival and a borderline improvement in overall survival in the experimental regional treatment program, compared to the all-intravenous therapeutic regimen (Table 2).

The most recently reported randomized ovarian cancer regional chemotherapy study again compared intravenous to intraperitoneal cisplatin, but patients in the intraperitoneal chemotherapy arm were also administered intraperitoneal paclitaxel.[37] All patients in the trial received intravenous paclitaxel. As with the previously discussed study, the largest size of any residual mass permitted entry into this trial was 10 mm. This study revealed a statistically significant 16-month median improvement in overall survival associated with the regional therapy program, in addition to a documented improvement in progression-free survival.

Table 2 Phase 3 randomized trials comparing intraperitoneal (ip) versus intravenous (iv) cisplatin-based drug delivery employed as primary chemotherapy of small-volume residual advanced epithelial ovarian cancer

	Progression-free survival (median)	Overall survival (median)
ip versus iv cisplatin (all patients also received iv cyclophosphamide)[35]	–	48 vs 41 months (p = 0.02; HR 0.76)
ip versus iv cisplatin[a] (all patients also received iv paclitaxel)[36]	28 vs 22 months (p = 0.01; HR 0.78)	63 vs 52 months (p = 0.05; HR 0.81)
ip versus iv cisplatin[b] (all patients also received iv paclitaxel)[37]	23.8 vs 18.3 months (p = 0.05; HR 0.77)	65.6 vs 49.7 months (p = 0.03; HR 0.73)

[a]Patients in the ip treatment arm also received two cycles of moderately high dose iv carboplatin prior to the delivery of regional chemotherapy.
[b]Patients in the ip treatment arm received ip paclitaxel in addition to ip cisplatin.

The intraperitoneal regimen was found to cause more toxicity and less than one half of the treated patient population was able to complete the entire planned 6 treatment cycles. Of interest, this study included a prospective evaluation of measures of quality of life. This analysis revealed inferior quality of life associated with the regional program during therapy, but importantly at 1-year follow-up there was essentially no difference between the two study arms.

One highly provocative question resulting from this third randomized trial is the issue of whether the documented improvement in overall survival observed following intraperitoneal drug delivery might have been even greater if a higher percentage of women had been able to receive the entire planned 6 treatment courses. Alternatively, it could be argued that the majority of the benefits achieved from regional platinum delivery may be observed if women are administered only 3 or 4 such cycles. Again, these questions remain interesting hypotheses that may be tested in future phase 3 randomized trials.

Rational use of intraperitoneal chemotherapy in epithelial ovarian cancer

Based on existing data, where is it appropriate to consider the use of intraperitoneal chemotherapy in the routine management of ovarian cancer?

Existing evidence-based (randomized phase 3 trial) data provide strong support for the conclusion that patients with small volume residual advanced ovarian cancer (largest tumor mass <10 mm in maximum diameter) should be offered the option to receive a cisplatin-based intraperitoneal strategy, assuming there are no medical contraindications to receiving cisplatin (eg, renal insufficiency; pre-existing neuropathy) or to receiving regional treatment (eg, presence of extensive adhesions at the time of prior surgery).[35–37,39,40] Further, while a patient can certainly elect to not receive this treatment, based on the time, effort, and potential additional morbidity associated with the approach, it can also be argued that oncologists whose particular practice setting prevents their being able to offer such therapy should consider referral (where feasible) of an ovarian cancer patient who may benefit from intraperitoneal drug delivery to an oncology practice where this strategy can be administered.

Intraperitoneal chemotherapy may also be rationally offered to women with advanced ovarian cancer who have been managed primarily with a neoadjuvant approach, but where an initial excellent response to chemotherapy has led to surgery and no or minimal residual tumor volume following the completion of this interval cytoreductive procedure.[41] Here one can argue that the high local concentrations achievable with intraperitoneal treatment may potentiate the effects of the chemotherapeutic agents already documented to be highly biologically active in the particular individual's cancer. The ultimate benefits of this approach compared to the continuation of systemic chemotherapy is worthy of investigation in a phase 3 randomized trial. Of note, such a trial is currently planned to be conducted by the Gynecologic Cancer Intergroup, an international consortium of gynecologic cancer clinical investigators.

Intraperitoneal anti-neoplastic drug delivery may also be considered in the setting of an ovarian cancer patient with a high grade malignancy who has achieved a surgically defined complete response to primary systemic chemotherapy, where it is known the ultimate risk of recurrence is very high. While interesting phase 2 trial data supporting this approach have been presented,[42] the few very underpowered phase 3 trials that were designed to evaluate this approach have not provided evidence for the utility of this form of consolidation therapy.[43]

Based on the results of the previously noted non-randomized phase 2 trials examining platinum-based second-line therapy in ovarian cancer, it is not unreasonable to consider this strategy in a woman who has achieved a major partial response following primary systemic platinum chemotherapy.[11,44–46] However, again, no randomized phase 3 trial data are available to demonstrate the superiority of this approach compared to continuation of systemic therapy.

Finally, as it is known that patients with "high risk" early stage ovarian cancer have a 30% to 50% chance of experiencing recurrence of the disease process, and those recurrences are largely within the peritoneal cavity, it is perhaps reasonable to consider delivering some, or perhaps all, of a planned adjuvant chemotherapy approach via the intraperitoneal route. As previously stated, the administration of either intraperitoneal cisplatin or carboplatin will lead to adequate systemic drug concentrations, and also substantially higher platinum concentrations within the peritoneal cavity.

A role for intraperitoneal carboplatin

As outlined within this text, the large majority of currently reported trials examining regional drug delivery in ovarian cancer have employed cisplatin, rather then carboplatin. This is largely due to the fact the early studies of intraperitoneal chemotherapy were initiated before the widespread use of carboplatin, and subsequent evidence of the equivalence

of the two platinum drugs when delivered systemically in advanced ovarian cancer.

Is it reasonable to simply substitute carboplatin in any regimen where cisplatin has been utilized?

Extensive experience with systemically administered carboplatin in ovarian cancer has revealed the two agents have essentially equivalent biological activity, but with quite different toxicity profiles.[47–49] The modestly reduced potential for the development of neuropathy associated with carboplatin, compared to cisplatin, is particularly relevant when the platinum agent is combined with another neurotoxic drug, such as a taxane. A "carboplatin plus paclitaxel" chemotherapy regimen is easily administered in the out-patient setting, and this program continues to be an overwhelmingly favorite primary strategy among oncologists treating women systemically for ovarian cancer.

As previously noted, phase 2 trials of intraperitoneal carboplatin in ovarian cancer have reported favorable survival and toxicity outcomes, but there remains a notable absence of randomized phase 3 trial data employing the newer platinum drug delivered by this route. The GOG plans to examine intraperitoneal carboplatin in a phase 3 trial in the future, but it is unknown at this point in time when data from this experience will be available.

For the present, it is reasonable to consider several options when contemplating the use of intraperitoneal carboplatin in ovarian cancer:[50,51]

1. Substitution of carboplatin for cisplatin in all patients receiving intraperitoneal chemotherapy:
   While certainly not an irrational option, if an oncologist elects to simply substitute carboplatin for cisplatin, for example in a patient with small volume residual advanced ovarian cancer after primary surgical cytoreduction, it is incumbent upon the physician to inform the patient that the evidence-based studies that documented the utility of regional therapy actually employed cisplatin. Further, the specific justification for utilizing carboplatin, rather than cisplatin, should be explained to the patient.
2. Substitution of carboplatin if excessive toxicity with cisplatin is observed:
   In this situation, the physician will attempt to initially deliver intraperitoneal cisplatin but if the patient experiences excessive side effects (eg, emesis), the next course can be administered with intraperitoneal carboplatin. One can rationally argue that if the choice is between switching therapy to either intravenous carboplatin or intraperitoneal carboplatin, there is no reason to believe regional carboplatin delivery will be less effective, and

it may be more effective than systemic administration of the agent.

3. Plan to deliver a limited number of courses of both intraperitoneal cisplatin and carboplatin:
   This strategy recognizes the fact it is difficult for the majority of patients to tolerate 6 cycles of a cisplatin-based intraperitoneal chemotherapy program, despite the fact the data demonstrating a survival benefit were based on delivery of this agent. Thus, it might be planned that a woman with small volume residual advanced ovarian cancer will be treated with 2 to 3 cycles of intraperitoneal cisplatin (depending on tolerability), and then switched to intraperitoneal carboplatin (3–4 cycles) to complete the treatment program.

The optimal dose of intraperitoneal carboplatin also remains to be defined, but on the basis of existing data (both systemic and regional) it is rational to propose delivering the agent by this route at an AUC (area-under-the-concentration-versus-time curve) of 5 or 6.[14,47–51]

Conclusion

The intraperitoneal delivery of cisplatin has been demonstrated in several evidence-based randomized phase 3 trials to improve overall survival when employed as first-line chemotherapy treatment of women with small volume residual advanced ovarian cancer. Despite this fact, many oncologists remain reluctant to routinely employ this approach, often because of the well-recognized systemic toxicity associated with cisplatin.

The use of intraperitoneal carboplatin has a particular appeal in this setting, as the drug is well established as the primary platinum agent employed in the management of women with ovarian cancer, and it has been documented to have a more favorable toxicity profile compared to the older platinum. Another very pragmatic attraction of intraperitoneal carboplatin is that use of the agent makes it easier to deliver regional therapy in the setting of a busy oncology practice (eg, less actual required treatment time; reduced risk of troublesome toxicities). Unfortunately, there remain no phase 3 trial data documenting the equivalence of intraperitoneal cisplatin and carboplatin, or the superiority of intraperitoneal carboplatin compared to intravenous carboplatin.

Planned trials will hopefully provide definitive answers to this important question. For the present, it is not unreasonable to employ intraperitoneal carboplatin in the management of ovarian cancer after considering the limitations of existing data, and the potential toxicity of cisplatin-based therapy that may be, or has been, encountered in an individual patient.

Disclosures

The author has no conflicts of interest to disclose.

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