Point: Intraperitoneal Chemotherapy in the Management of Ovarian Cancer

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Ovarian cancer, cisplatin, carboplatin, intraperitoneal chemotherapy

Abstract
Both preclinical considerations and results of phase I safety and pharmacokinetic studies provided support for the argument that intraperitoneal antineoplastic drug delivery should be a rational approach to the management of ovarian cancer. Subsequently conducted phase II trials exploring regional treatment revealed surgically documented objective responses when the approach was employed as a second-line therapy. Recently, the results of three randomized phase III trials have shown that the use of primary cisplatin-based intraperitoneal therapy leads to superior survival compared with intravenous cisplatin-based treatment in patients with small-volume residual advanced ovarian cancer after initial surgical cytoreduction. Further exploration of this unique management strategy is indicated to develop an optimal approach that maintains the demonstrated enhanced efficacy while reducing the toxicity (principally because of cisplatin) of treatment. (JNCCN 2004;2:549–554)

Rationale for Intraperitoneal Chemotherapy
The fundamental goal of intraperitoneal treatment of ovarian cancer is to expose malignant cells present within the cavity to higher concentrations of drug (e.g., peak levels) for longer periods of time (e.g., total area-under-the-concentration-versus-time curve [AUC]) than possible with systemic administration. Preclinical drug modeling studies, anatomic considerations (e.g., drug uptake from the cavity principally via the portal circulation), and knowledge of the natural history of ovarian cancer (e.g., the malignancy remains clinically confined to the cavity in most individuals for extended periods of time) lead researchers to conclude that this is a highly rational management approach, worthy of clinical investigation.

Furthermore, in vitro evaluation of a number of drugs with known activity in ovarian cancer had suggested that substantially enhanced cytotoxicity might be seen at the concentrations of drug possibly safely achievable after intraperitoneal delivery, but not with systemic administration.3

Limitations of Intraperitoneal Therapy
Despite the fact the intraperitoneal administration of antineoplastic agents as therapy for ovarian cancer was initially examined as a therapeutic strategy almost 50 years ago, it has only been within the past decade that definitive randomized phase III trials have shown the favorable impact of this unique strategy on survival. This review briefly outlines the rationale and practical and theoretical limitations of regional drug delivery in the treatment of ovarian cancer, and then discusses the results of clinical studies using this therapeutic strategy.

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a maximum of several millimeters from the surface of the peritoneal lining.5–9 These data strongly argue that any enhanced tumor-drug interactions potentially achievable with intraperitoneal instillation will only be relevant for patients with limited tumor volumes (e.g., microscopic disease or tumor nodules less than 0.5 cm in maximum diameter).

In addition, the local toxicity of regional therapy (e.g., abdominal pain, adhesion formation leading to bowel obstruction) may result in this technique being unacceptable for a particular agent, despite a strong pharmacokinetic rationale (e.g., more than 2-log increased exposure of cancer within the cavity).

A final important issue relates to the concern that although instilling antineoplastic agents into the peritoneal cavity may lead to a major increase in local exposure, the overall effectiveness of treatment may be diminished because of reduced delivery of drug to tumor though the vascular compartment by capillary flow. Phase I pharmacokinetic and safety studies have shown that when certain agents (including cisplatin and carboplatin) are delivered into the peritoneal cavity, minimal local toxicity occurs, such that the dose-limiting toxicities are the systemic effects of the drugs (e.g., emesis, nephrotoxicity; neurotoxicity for cisplatin; bone marrow suppression for carboplatin).10–13 This observation leads to the logical conclusion that systemic exposure (and subsequent delivery of drug to tumor by capillary flow) does not need to be compromised with regional treatment, assuming that appropriate doses are administered to achieve optimal serum concentrations. In contrast, for other agents for which local toxicity (e.g., abdominal pain) limits the amount of systemic exposure, the drug may need to be delivered intravenously to insure the desired therapeutic effect.14,15

Phase I Trials of Intraperitoneal Therapy
A large number of cytotoxic and biologic agents have been explored for their safety and pharmacokinetic advantage when delivered using the intraperitoneal route.4 A representative sample of drugs examined with demonstrated activity in ovarian cancer, and the resulting pharmacokinetic profiles seen, are outlined in Table 3.

Of note, the regional delivery of both carboplatin and cisplatin leads to a 10- to 20-fold increased exposure of the peritoneal cavity to active drug, without any reduction in the level of the agent present within the systemic compartment.11–13 However, although there is a rather profound increase in local drug concentrations (more than 1000-fold compared with the systemic circulation) after the intraperitoneal administration of paclitaxel, very limited levels of the agent are detected in the blood.14,16 This is because of both hepatic metabolism of paclitaxel (after uptake into the portal circulation) and drug-associated peritoneal irritation (defining the maximal concentration that can be safely instilled into the cavity).

Phase II Trials of Intraperitoneal Chemotherapy in Ovarian Cancer
Over the past two decades, multiple phase II efficacy trials involving regional drug delivery have been conducted in patients with advanced ovarian cancer.14,17

Table 1 Practical Issues With Intraperitoneal Therapy

- Drug-associated peritoneal irritation leading to pain, adhesion formation, and subsequent bowel obstruction
- Adequacy of drug distribution after regional delivery
- Development of convenient and cost-effective access to the peritoneal cavity
- Complications associated with catheter systems (e.g., infections, bowel obstruction)

Table 2 Theoretical Objections to Intraperitoneal Therapy

- Limited direct penetration of drugs into tumor tissue
- Reduction of delivery of agents to tumor by capillary flow

Table 3 Pharmacokinetic Advantage Associated With Intraperitoneal Antineoplastic Drug Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ratio of peak concentration between peritoneal cavity and systemic compartment</th>
</tr>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>20</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1000</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>300</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>470</td>
</tr>
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These trials have explored both single agent and combination therapy regimens. As might have been anticipated, because of its central role in the management of this malignancy, cisplatin has been the drug most commonly evaluated. Furthermore, the large majority of published phase II studies have involved ovarian cancer patients treated in the “second-line” setting, either in women with documented persistent disease after completion of primary treatment or in the presence of recurrent cancer.

When examined as second-line therapy, surgically documented responses (laparotomy or laparoscopy), including complete remissions, have been shown.18–29 Furthermore, prolonged disease-free and overall survival has been seen in a subset of such patients.30–33 As predicted by the previously noted preclinical data regarding depth of drug penetration, both the highest objective response rates and longest survivals have been noted in women with the smallest tumor volumes (e.g., microscopic disease only when second-line intraperitoneal therapy was initiated).18

Unfortunately, to date, no randomized phase III trials have been conducted comparing intravenous versus intraperitoneal second-line therapy in ovarian cancer. Thus, it remains uncertain if the provocative high response rates and prolonged survival seen in phase II trials result from a genuine improvement in outcome because of regional treatment or merely reflect the overall natural history of disease in this subset of patients with recurrent or persistent ovarian cancer after systemically-delivered primary platinum-based chemotherapy.

**Phase III Randomized Trials of Primary Intraperitoneal Chemotherapy in Advanced Ovarian Cancer**

Despite the absence of information from definitive trials evaluating the benefits of regional therapy delivered in the second-line setting, firm data now exist from several phase III randomized trials of intraperitoneal chemotherapy used as primary chemotherapy of advanced ovarian cancer that both showed the favorable impact of this strategy on overall survival in the malignancy and defined a rational direction for future research in this area.

In the mid-1980s, the Southwest Oncology Group (SWOG) and the Gynecologic Oncology Group (GOG) initiated a randomized phase III trial that compared intravenous cisplatin to intraperitoneal cisplatin (both delivered at a dose of 100 mg/m²) when employed as primary chemotherapy for small volume (largest residual mass less than 2 cm in maximal diameter) residual advanced ovarian cancer after an attempt at surgical cytoreduction.14 All patients also received intravenous cyclophosphamide (600 mg/m²). The results of this study, published in a 1996 landmark paper in the *New England Journal of Medicine*, revealed that the regional treatment program resulted in a statistically significant improvement in overall survival (49 months vs. 41 months; \( P = .02 \); hazard ratio 0.76), compared with intravenous drug delivery.14 Furthermore, although (as anticipated) more abdominal discomfort was associated with intraperitoneal instillation (generally short-lived, mild or moderate in severity, and not interfering with further treatment), patients treated with regional delivery actually experienced less neutropenia and tinnitus than those undergoing systemic treatment.

Although the results of this trial were acknowledged to be important, the absence of paclitaxel from the regimen (which was not available when this trial was initiated), raised the question of whether the substitution of intravenous paclitaxel for cyclophosphamide (in both study arms) would have negated any additional benefits of regional cisplatin administration.

As a result, a second phase III randomized trial examining intraperitoneal therapy as primary treatment of small-volume residual advanced ovarian cancer was initiated by the GOG, SWOG, and the Eastern Cooperative Oncology Groups. In this trial, the largest residual tumor nodule after surgery must have been less than 1 cm in maximal diameter.16 The study compared intraperitoneal versus intravenous cisplatin, with all patients also receiving intravenous paclitaxel. Individuals randomized to the experimental study arm were initially given two courses of moderately high-dose intravenous carboplatin (AUC 9), in an effort to “chemically debulk” any residual macroscopic cancer before employing regional drug delivery. This strategy was designed to take maximum advantage of the high local concentrations in direct contact with residual tumor cells present within the peritoneal cavity.

Unfortunately, the two courses of intravenous carboplatin were associated with excessive bone marrow suppression (principally thrombocytopenia), resulting in almost 20% of patients in the experimental
study arm receiving two courses or less of the regional treatment. Discontinuation of therapy was mainly because of persistent hematologic abnormalities. Despite this fact, the intraperitoneal regimen was associated with a statistically significant improvement in both progression-free (28 vs. 22 months; \(P = .01\)) and overall survival (63 vs. 52 months; \(P = .05\); hazard ratio, 0.81). Because of the toxicity of the specific regimen (moderately high-dose intravenous carboplatin followed by intraperitoneal cisplatin), the investigators did not recommend it in future trials. However, this study again revealed the favorable impact of cisplatin-based intraperitoneal therapy on survival in this clinical setting.

The preliminary results of a third phase III randomized trial, conducted by the GOG, have provided additional support for the conclusion that intraperitoneal therapy is a highly rational management approach in the treatment of ovarian cancer. This trial compared a “control arm” of intravenous cisplatin plus intravenous paclitaxel to an experimental regimen of intraperitoneal cisplatin and both intravenous and intraperitoneal paclitaxel. Although the investigative regimen was associated with greater toxicity (particularly bone marrow suppression, presumably because of the added paclitaxel reaching the systemic compartment), progression-free survival was substantially improved (hazard ratio: 0.73) in the regional delivery study arm. Data on overall survival in this trial are awaited with considerable interest.

Future Directions for Clinical Research Involving Intraperitoneal Chemotherapy in Ovarian Cancer

Based on the results of three well-designed and conducted randomized phase III clinical trials revealing improved survival associated with regional drug delivery used as primary chemotherapy of small-volume residual advanced ovarian cancer, it is no longer tenable to simply dismiss, as some continue to do, a possible role for intraperitoneal therapy in the management of ovarian cancer. However, despite these results, regional drug delivery is rarely (if ever) employed outside the study setting. Why?

Several possible explanations may be advanced, including the additional time and effort associated with intraperitoneal instillation and increased risk of local morbidity (e.g., catheter-associated infection); however, the major issue is probably the continued use of cisplatin in this clinical setting. In striking contrast to the use of carboplatin, cisplatin administration results in a substantially increased risk of emesis (and associated decreased quality-of-life) and need for extensive hydration, and when it is delivered with paclitaxel, the later agent must be delivered over 24-hours (to reduce the risk of serious peripheral neuropathy).

If carboplatin could be successfully substituted for cisplatin when employed as primary therapy of ovarian cancer, there would almost certainly be greater acceptance for the regimen among practicing oncologists and their patients. Of interest, single-agent intraperitoneal carboplatin has been explored for efficacy in the phase II setting when employed as second-line therapy of ovarian cancer, with surgically documented responses being seen. As previously noted, the pharmacokinetic advantage of the agent is similar to that of cisplatin, and local toxicity is minimal.

What remains unavailable are data from a well-designed randomized trial to confirm (or refute) the survival benefits associated with intraperitoneal compared with intravenous carboplatin, when combined with intravenous paclitaxel, as primary therapy of ovarian cancer. This exact study design is planned by the GOG in the near future.

Current Role for Intraperitoneal Chemotherapy in the Management of Ovarian Cancer

Based on existing data, defining a precise role for intraperitoneal drug delivery in the routine management of ovarian cancer is not possible. An individual oncologist could certainly reasonably argue that primary chemotherapy of small-volume residual advanced disease should use the intraperitoneal route. However, as previously noted, this would currently require the administration of cisplatin rather than carboplatin.

Alternatively, also reasonable would be consideration of administration of either intraperitoneal cisplatin or carboplatin as a management strategy in women with very small-volume persistent disease, documented at the time of a second-look laparotomy or laparoscopy after an initial response to systemic platinum-based chemotherapy. Here the major concern is the existence of extensive phase II trial information, but a complete absence of data from phase III randomized studies comparing this strategy to that of
systemic drug administration exists. Physician judgment and experience and patient choice should help guide management in this clinical circumstance.

Conclusions
What is perhaps most striking regarding the issue of regional treatment of patients with ovarian cancer is the length of time from the initial exploration of this method, in the 1950s, until the present, and the continued uncertainty regarding a role for this method of drug delivery in standard management of ovarian cancer. Despite this extensive delay in finding the answer, however, accumulating data provide increasingly strong support for the conclusion that carefully selected patients with ovarian cancer will experience superior survival if treated by the intraperitoneal route. It is reasonable to anticipate that future clinical research efforts in this area will more carefully define the optimal patient populations to receive this form of therapy and the treatment regimens to administer in this setting.

References


