Is There a Role for Intraperitoneal Chemotherapy in the Management of Ovarian Cancer

By Maurie Markman, MD [2]

Phase I and II clinical trial data have demonstrated the safety, pharmacokinetic advantage, and potential for enhanced cytotoxicity associated with the intraperitoneal administration of antineoplastic agents in the

Introduction

What role, if any, should intraperitoneal chemotherapy play in the management of ovarian cancer? It is rather remarkable that this question must be asked after more than 2 decades of clinical investigation.[1,2] Perhaps we should first inquire as to why it has taken so long to answer this question.

History of Intraperitoneal Therapy for Ovarian Cancer

In the earliest days of the modern chemotherapeutic era (1950s), it was recognized that the direct delivery of cytotoxic agents into the peritoneal cavity had the potential to be a clinically useful approach in the treatment of malignancies principally confined to this body compartment.[3,4] However, it was only with the publication of a pharmacokinetic modeling study by Dedrick et al in the late 1970s that a sound theoretical rationale for this approach in the management of ovarian cancer was presented.[1]

Simply stated, this model predicted that for certain cytotoxic agents, higher concentrations and longer durations of tumor exposure could be achieved with the intraperitoneal, rather than systemic, delivery of the same drug. This article stimulated considerable interest in the concept of regional therapy with antineoplastic drugs in the treatment of ovarian cancer, and subsequently, numerous phase I and II trials of single-agent and combination intraperitoneal chemotherapies were conducted.[2,5-7]

These studies, conducted during the 1980s and early 1990s, revealed a major pharmacokinetic advantage associated with the regional delivery of selected antineoplastic agents (Table 1).[2,5-7] and established the feasibility and safety of this approach. These studies also demonstrated that surgically defined complete responses and long-term survival could be observed following cisplatin (Platinol)-based intraperitoneal therapy delivered in the second-line setting in patients with ovarian cancer (Table 2).[8-16]

Unfortunately, these studies failed to provide a definitive answer to the question asked in the title of this article: Is there a role for intraperitoneal chemotherapy in the management of ovarian cancer? In fact, this question could only be answered directly through well-designed randomized phase III studies, the results of which were not available until relatively recently.

Phase III Trials of Intraperitoneal Therapy as Initial Management of Ovarian Cancer

Table 3 lists the regimens studied in the few phase III trials of intraperitoneal therapy in the initial management of ovarian cancer.

Cisplatin Plus Cyclophosphamide

In 1996, investigators from the Southwest Oncology Group (SWOG) and the Gynecologic Oncology
Group (GOG) published the results of the first large randomized phase III trial comparing intraperitoneal chemotherapy to standard intravenous (IV) chemotherapy in the treatment of advanced ovarian cancer. In this landmark study, more than 600 patients, whose largest residual intraperitoneal tumor mass was < 2 cm in maximum diameter, were randomized to receive either IV or intraperitoneal cisplatin (100 mg/m²). All patients were also treated with IV cyclophosphamide (Cytoxan, Neosar) 600 mg/m².

**Toxicity:** As anticipated, there was more abdominal discomfort in the patient population receiving the intraperitoneal program than the IV approach. However, in the majority of treated individuals, this discomfort was temporary and patients were able to continue with the planned treatment program.

Of some surprise, the study revealed a statistically significant reduction in both neutropenia and ototoxicity associated with the regional treatment regimen. Overall, however, there were no major differences between the two treatment arms in terms of severe toxicity, including treatment-related deaths or removal from the study due to side effects. The toxicity data generated in this study were of interest, particularly considering the "learning curve" required by both surgeons and medical oncologists participating in this trial (many of whom had never previously administered intraperitoneal chemotherapy).

**Survival:** The study was most notable for the overall survival results of the two treatment arms. There was a statistically significant improvement in overall survival associated with the intraperitoneal cisplatin arm—49 months for the intraperitoneal arm vs 41 months for the IV arm ($P = .02$). This outcome translated into approximately a 22% reduction of relative risk of death. To place these results into perspective with other currently accepted standard-of-care interventions, the relative risk reduction observed in this important intraperitoneal trial is comparable to that observed with the use of adjuvant tamoxifen (Nolvadex) for women with node-positive breast cancer.

Thus, it is now appropriate to ask: If the results of this randomized trial were so favorable, why did the oncology community not embrace them and begin using intraperitoneal therapy as a standard treatment approach in small-volume residual advanced ovarian cancer? While several possible answers might be provided, perhaps the most likely is the fact that this study did not include the use of paclitaxel (Taxol) in either the control or experimental treatment arm.

**Cisplatin, Paclitaxel, and Carboplatin**

The role of paclitaxel in the standard initial management of ovarian cancer had not been demonstrated at the time the aforementioned randomized intraperitoneal study was initiated. Thus, investigators questioned whether the favorable results associated with the use of intraperitoneal cisplatin would still be achievable in a regimen that included paclitaxel (rather than cyclophosphamide). Therefore, researchers from SWOG, GOG, and the Eastern Cooperative Oncology Group (ECOG) conducted a second randomized, controlled trial examining the clinical utility of intraperitoneal vs intravenous cisplatin in patients with small-volume residual advanced ovarian cancer, but this time also administered IV paclitaxel to all patients as a component of the treatment program.

Before discussing the results of this trial, several additional features of this study should be noted. First, the maximum tumor diameter permitted for entry into this trial was only 1 cm, compared to 2 cm for the previously discussed study. Presumably, this clinical feature would improve the survival outcome for both treatment arms. Second, the investigators attempted to optimize the chances that the high local concentrations of cisplatin present within the peritoneal cavity following regional delivery could be translated into a favorable outcome by administering two courses of moderately high-dose IV carboplatin (Paraplatin) prior to the initiation of the regional program. It was hypothesized that this IV therapy could "chemically debulk" the tumor, thereby decreasing the size of any residual tumor masses before the administration of intraperitoneal cisplatin.

**Results:** To date, the outcomes associated with this randomized trial have been presented only in abstract form. However, the preliminary results provide additional data regarding a potential role of intraperitoneal drug delivery in the management of small-volume residual advanced ovarian
cancer.

Unfortunately, the two courses of moderately high-dose carboplatin were associated with severe bone marrow suppression, particularly thrombocytopenia, which resulted in 19% of patients in the experimental arm receiving two or fewer courses of intraperitoneal therapy. In addition, gastrointestinal toxicity was significantly greater in the experimental treatment arm. Consequently, the experimental regimen could not be delivered as initially planned in a substantial percentage of individuals, thereby potentially reducing the impact of regional drug delivery on the ultimate outcome.

Nevertheless, use of the intraperitoneal program was found to be associated with a statistically significant improvement in progression-free survival (28 vs 22 months, \( P = .01 \)) and a borderline improvement in overall survival (63 vs 52 months, \( P = .05 \).[20] The relative risk reduction for death (19%) was remarkably similar to that seen in the previously discussed randomized intraperitoneal chemotherapy study,[6] a finding that provides strong support for the general conclusions regarding the effectiveness of regional therapy observed in the individual trials.

Investigators of this second randomized intraperitoneal study appropriately concluded that the survival advantage associated with this regimen could not justify the level of toxicity. Consequently, they recommended that this specific program not be employed in standard clinical practice or considered for further clinical development. However, despite the observed toxicity, the results of this study continued to stimulate interest with regard to defining a role for intraperitoneal drug delivery in ovarian cancer.

**Cisplatin Plus Intraperitoneal Paclitaxel**

To further explore this potential, GOG investigators subsequently initiated a third randomized intraperitoneal trial, this time examining an experimental regimen containing intraperitoneal cisplatin and both intravenous and intraperitoneal paclitaxel. The study arm of this trial was again compared to a control arm of IV cisplatin and IV paclitaxel.

The use of intraperitoneal paclitaxel in this trial was based on the impressive pharmacokinetic advantage (> 1,000-fold increased exposure of the peritoneal cavity vs the systemic compartment) noted with the regional delivery of the agent.[22,23] In addition, previously reported phase II data had revealed that the intraperitoneal administration of paclitaxel, employed as second-line therapy for ovarian cancer, was associated with a high surgically documented complete response rate in patients with microscopic disease only at the initiation of the regional treatment program.[24]

**Results:** Preliminary results of this ongoing randomized intraperitoneal chemotherapy trial are anticipated within the next 2 years. These results should help define a role for regional treatment in the front-line management of small-volume residual advanced ovarian cancer. This study is particularly relevant because it utilizes the intraperitoneal route to administer both the most active drug in ovarian cancer (a platinum agent) and the drug with the most profound pharmacokinetic advantage for cavity exposure (paclitaxel) following regional delivery.

**Why Is Intraperitoneal Chemotherapy Not Used as Initial Treatment of Ovarian Cancer?**

The encouraging results of the two published randomized trials discussed above might suggest that intraperitoneal therapy should be employed as initial therapy of ovarian cancer.[17,20] After all, when the only randomized trials for other tumor types have revealed improvements in progression-free and overall survival, the treatment regimens utilized in these studies have normally been incorporated into standard clinical practice.

It might be argued that the time, effort, and morbidity associated with intraperitoneal therapy prevents physicians from using this strategy. There is little question that regional therapy does require additional time and effort on behalf of both the patient and physician. However, even more complex management strategies (eg, the self-administration of bone marrow colony-stimulating...
factors, requirement of hospitalization for neutropenic fever) have been easily incorporated into standard oncologic treatment regimens when they appear to improve clinical outcome. Regarding the issue of increased toxicity associated with regional treatment, the results of the previously discussed randomized trials have failed to demonstrate a major increase in serious morbidity specifically associated with the intraperitoneal administration of cisplatin.[17,20]

Therefore, it is unlikely that the lack of acceptance of intraperitoneal therapy is based solely on the increased complexity and toxicity associated with regional treatment. In fact, it is possible that much of the reluctance to employ this management strategy is due to the apparent requirement that cisplatin be used rather than carboplatin.

**Carboplatin vs Cisplatin**

Currently in the United States, the large majority of women with advanced ovarian cancer receive a regimen of IV carboplatin and paclitaxel (in a 3-hour infusion). This regimen is used both because of its demonstrated efficacy in phase III randomized trials and its more favorable toxicity profile compared to cisplatin and paclitaxel (in a 24-hour infusion).[25,26] (When cisplatin is employed at a standard dose level of 75 mg/m$^2$, paclitaxel must be administered as a longer infusion [24 hours] due to the development of a serious neurotoxicity observed with the shorter [3-hour] paclitaxel regimen.[27-29])

Thus, in the intraperitoneal cisplatin program, patients not only have to experience the greater systemic toxicity associated with cisplatin (eg, emesis, nephrotoxicity, neurotoxicity), but also must receive a more complex paclitaxel treatment schedule. Is it any wonder oncologists would rather use the IV carboplatin/paclitaxel regimen? Nevertheless, we still must ask whether it might be possible to substitute intraperitoneal carboplatin for cisplatin when employed as front-line therapy for ovarian cancer.

**Substituting Carboplatin for Cisplatin**

Previously reported phase I and II trials have revealed a similar pharmacokinetic profile between carboplatin and cisplatin following regional delivery.[30,31] In addition, carboplatin produces only mild local toxicity with intraperitoneal administration, and surgically documented responses (including complete responses) have been observed following this route of treatment with carboplatin.[32,33]

While limited preclinical data have suggested that higher intratumoral levels of platinum are achieved following the intraperitoneal administration of cisplatin[34-36] vs carboplatin, the clinical relevance of this observation is unknown.[37] However, it is reasonable to suggest that if intraperitoneal treatment is ever to become a routine treatment approach in ovarian cancer, it will be critical to determine whether the less toxic platinum agent (carboplatin) can replace cisplatin in the therapeutic regimen. This may ultimately necessitate a randomized, controlled trial to directly compare the two platinum-based intraperitoneal regimens. Interest in the development of such a study will be greatly influenced by the results of the previously discussed ongoing GOG trial.

**Second-Line Therapy Using the Intraperitoneal Route**

The greatest experience with intraperitoneal therapy for ovarian cancer has been with agents employed as second-line treatment of very small-volume disease following an initial response to standard IV chemotherapy.[2] Surgically documented responses, including complete responses, have been observed with numerous agents delivered in this clinical setting. In addition, prolonged survival of more than 5 years has been reported for a subset of patients (ie, those with microscopic disease only or with a largest residual tumor mass < 0.5 cm in maximum diameter) who were given intraperitoneal cisplatin as a second-line treatment strategy.[15,16]

Unfortunately, there are no randomized trials that demonstrate the superiority of the regional approach to ovarian cancer, compared with IV delivery. A retrospective review of the ovarian cancer literature suggests that patients with small-volume residual disease at second-look surgery may
have a higher rate of surgically defined complete response at the time of a third-look surgical procedure if treated with intraperitoneal, rather than intravenous, cisplatin.[38] It is important to note, however, that such an analysis cannot substitute for data from a well-designed randomized, controlled clinical trial that directly addresses this important clinical issue.

Even in the absence of such data, it is reasonable to suggest that certain carefully selected patients might be appropriate candidates for a second-line intraperitoneal treatment strategy. Examples of such patient populations are outlined in Table 4.

It should be emphasized that any patient being considered for intraperitoneal therapy in this setting must be fully informed regarding the lack of definitive data demonstrating the efficacy of this approach. That said, the absence of critically relevant information from randomized trials does not negate the potential benefits of such therapy in individual patients.

**Consolidation Therapy Using the Intraperitoneal Route**

In my opinion, the use of intraperitoneal chemotherapy as a consolidation strategy in patients with either a clinically defined or (more appropriately) surgically defined complete response is a rational application of data generated from a number of well-conducted phase II second-line intraperitoneal chemotherapy trials. Several studies have demonstrated that the highest surgically documented complete response rate to intraperitoneal cisplatin-based chemotherapy occurs in patients with no more than microscopic residual disease at the time of a second-look laparotomy.[2,8] In addition, it is known that even after a negative second-look surgery, the ultimate relapse rate is approximately 50% (particularly in patients with poorly differentiated tumors).[39]

Thus, it can be argued that in the presence of undetected residual microscopic disease in an individual with a previous major response to systemically delivered cytotoxic chemotherapy, the high concentrations of cisplatin that are achievable within the peritoneal cavity following regional therapy may translate into increased tumor cell kill and prolonged progression-free and overall survival. Unfortunately, no randomized trials have been reported to confirm (or refute) these theoretical arguments. However, a report from Memorial Sloan-Kettering Cancer Center (MSKCC) provides provocative phase II data to support this hypothesis.[40]

Beginning in the late 1980s, patients at MSKCC with advanced ovarian cancer who achieved a surgically documented complete response to systemically administered cisplatin-based chemotherapy were offered treatment with three courses of an intraperitoneal cisplatin/etoposide treatment regimen.[40] The same investigators subsequently compared the relapse rates for patients undergoing intraperitoneal consolidation and a control group of women with ovarian cancer[40] treated at MSKCC during the identical time period[40] who were also found to have no evidence of disease at a second surgical assessment, but who had not undergone the regional consolidation approach.

Such comparisons of treated vs historical control populations are always fraught with hazard because of the potential for selection bias in favor of the treated population. In fact, in this comparison, the control population actually had more favorable clinical characteristics (eg, a higher percentage of patients with stage I/II and optimal stage III disease). This most likely resulted from the selection bias of physicians suggesting that patients at greatest risk of recurrence receive the intraperitoneal consolidation strategy, while women with a perceived lower risk for recurrence would not be offered treatment in this investigational program.

Despite the more favorable clinical characteristics associated with the control population, the recurrence rate in this group was higher (54%) than in patients receiving intraperitoneal consolidation (39%). In fact, among the 18 individuals who were able to receive all three courses of the intraperitoneal cisplatin program, the relapse rate was only 28%.

Again, while certainly not definitive, these results provide support for the argument that intraperitoneal therapy should be carefully examined as a consolidation strategy in appropriately designed randomized trials for ovarian cancer. It may also be considered a rational strategy in
carefully selected patients outside the study setting.

Conclusions

Returning to the original question: Is there a role for intraperitoneal chemotherapy in the management of ovarian cancer? In my opinion, the answer is yes. However, as discussed in this article, the number of patients for whom this management strategy is rational will be limited, even if the ongoing randomized phase III trial of intraperitoneal cisplatin/paclitaxel ultimately produces favorable results.

The depth of penetration of the cytotoxic agents directly into tumor (or normal) tissue is very limited (probably < 1 to 2 mm from the surface of the peritoneal lining).[34,35,41-43] Thus, the relative advantage associated with the intraperitoneal treatment of ovarian cancer, compared to IV drug delivery, will likely be evident only in patient populations where microscopic or very small-volume macroscopic disease is present when the regional strategy is initiated. These conditions would apply when the approach is being used as either second-line therapy or initial treatment of ovarian cancer.

Furthermore, individuals with significant intra-abdominal adhesions that prevent complete access to the peritoneal cavity would not be appropriate candidates for regional chemotherapy even if they have other clinical characteristics that might make them appropriate candidates for this management strategy.

References:


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