INTRODUCTION

The concept of the intraperitoneal administration of antineoplastic agents in the management of ovarian cancer has attracted the interest of numerous investigators. In fact, alkylating agents, the first cytotoxic drugs to be introduced into clinical practice, were initially examined for intraperitoneal delivery in the early 1950s [1]. However, it was not until the late 1970s that both the problems and potential of regional drug administration in the treatment of ovarian cancer began to be thoroughly explored [1, 2]. An important event in the development of a rational strategy for the examination of intraperitoneal drug delivery was the publication of a now-classic paper by Dedrick et al., from the National Cancer Institute where, for the first time, a sound pharmacokinetic rationale for this approach in the management of ovarian cancer was presented [3].

PRACTICAL AND THEORETICAL CONSIDERATIONS ASSOCIATED WITH INTRAPERITONEAL TREATMENT OF OVARIAN CANCER

A number of both practical and theoretical concerns have been raised regarding intraperitoneal therapy of ovarian cancer and other malignancies [1, 2, 4-6]. These important issues are outlined in Tables 1 and 2.

INTRAPERITONEAL CISPLATIN TREATMENT OF OVARIAN CANCER

With regard to cisplatin, both preclinical and clinical data have firmly established that any benefits associated with employing the intraperitoneal route of drug delivery in the treatment of ovarian cancer are limited to a relatively well-defined small subset of patients with this malignancy (Table 3) [1, 2, 7]. For example, in a series of...
patients treated at the Memorial Sloan-Kettering Cancer Center (MSKCC) with combination cisplatin-based therapy as salvage treatment of advanced ovarian cancer. 32% (17/50) of individuals whose largest residual tumor mass measured ≤1 cm in maximum diameter at the initiation of intraperitoneal therapy achieved a surgically documented complete response, compared to only 5% (2/39) of patients with at least one tumor mass >1 cm in maximum diameter [7].

In this analysis performed at MSKCC, a second important feature was found to strongly predict response to salvage intraperitoneal cisplatin. Not considering the size of the largest residual tumor mass, patients who had previously responded to systemically delivered cisplatin achieved a 33% (17/52) surgically documented complete response rate, compared to only a 3% (1/37) complete response rate if the initial cisplatin-based intravenous treatment had not resulted in at least a partial response.

Even patients with very small-volume disease (largest tumor mass ≤1 cm in maximum diameter) at the initiation of salvage intraperitoneal cisplatin were unable to exhibit a significant response rate if they had failed to respond to systemic treatment (surgical complete response rate: 7% [1/14]). In contrast, for those patients whose largest tumor mass was ≤1 cm, who also had initially responded to intravenous cisplatin, the surgically documented complete response rate was 42% (15/36) (p < 0.025).

These data provide strong evidence that the 10- to 20-fold higher concentrations of cisplatin achievable within the peritoneal cavity following intraperitoneal drug administration are able to overcome some degree of drug resistance associated with tumors shown to be at least partially sensitive to the cytotoxic agent. However, these drug levels cannot achieve this goal in tumors with a high degree of inherent resistance, which is characterized at the clinical level by a failure of the cancer to exhibit at least a partial response to initial intravenous treatment.

**OTHER AGENTS EXPLORED FOR INTRAPERITONEAL DELIVERY IN OVARIAN CANCER**

In addition to cisplatin, a number of other cytotoxic and biological agents have been examined for safety and potential efficacy when delivered by the intraperitoneal route as salvage treatment of ovarian cancer. These include carboplatin, mitoxantrone, doxorubicin, mitomycin-C, 5-fluorouracil, methotrexate, thiopeta, paclitaxel, recombinant interferon-α, recombinant interferon-γ, interleukin 2 and tumor necrosis factor [1, 2, 8-12]. Combination regimens have also been explored. The interested reader is referred to the original publications for details of each trial.

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**Table 1. Practical concerns associated with intraperitoneal therapy of ovarian cancer**

<table>
<thead>
<tr>
<th>Concern</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>1. Need to develop intraperitoneal delivery systems which are easy to learn, convenient, safe and cost effective;</td>
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<td>2. Inability to distribute drug-containing fluid throughout the peritoneal cavity;</td>
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<td>3. Risk of catheter-associated subcutaneous and peritoneal cavity infections, bowel perforation and obstruction;</td>
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<td>4. Risk of chemotherapy-associated chemical peritonitis.</td>
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**Table 2. Theoretical concerns associated with intraperitoneal therapy of ovarian cancer**

1. Decreased delivery of cytotoxic agent(s) to tumor by capillary flow if treatment is delivered by the intraperitoneal, rather than intravenous, route;
2. Preclinical data demonstrating highly limited penetration of drugs directly into tumor (or normal) tissue, suggesting only very small tumor volumes can be treated by the intraperitoneal route; and
3. Even with “adequate drug distribution” following intraperitoneal delivery, concern that not all tumor-bearing surfaces will be exposed to the drug-containing fluid.

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**Table 3. Surgically defined complete response rate to “salvage” intraperitoneal cisplatin in small-volume residual advanced ovarian cancer (the MSKCC experience) [7]**

<table>
<thead>
<tr>
<th>Largest residual tumor mass</th>
<th>Prior response to systemic cisplatin</th>
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<tr>
<td>&lt; 0.5 cm*</td>
<td>Yes 43% (13/30) No 9% (1/11)</td>
</tr>
<tr>
<td>&lt; 1 cm**</td>
<td>Yes 42% (15/36) No 7% (1/14)</td>
</tr>
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</table>

* <0.05  ** <0.025

Surgically defined responses, including complete responses, have been observed with a number of agents and drug combinations delivered by the intraperitoneal route. Unfortunately, no randomized trial of intraperitoneal versus intravenous therapy in the salvage setting in patients with ovarian cancer has been reported. Therefore, it is reasonable to conclude that the ultimate impact of these responses on progression-free survival, overall survival, or quality of life in the patients with persistent disease, or developing recurrent ovarian cancer following initial intravenous therapy remains to be defined.

In the absence of randomized controlled trial data, and despite the evidence of clinical activity of intraperitoneal therapy (particularly cisplatin-based) in patients with ovarian cancer, there remained (and continues to remain) considerable skepticism as to the value of this strategy in the management of this malignancy. Reasonable criticisms of this therapeutic approach are outlined in Table 4.
**Intraperitoneal Cisplatin as Initial Treatment of Small-Volume Advanced Ovarian Cancer**

The recent preliminary report of a large intergroup randomized trial examining intraperitoneal cisplatin as initial treatment of ovarian cancer has muted much of this criticism and has renewed considerable interest in the intraperitoneal approach to the management of ovarian cancer [13].

More than 600 patients with small-volume residual stage III ovarian cancer (largest diameter disease following tumor debulking ≤2 cm) were randomized to receive either intravenous or intraperitoneal cisplatin. The dose of cisplatin in both treatment arms was 100 mg/m². All patients also received intravenous cyclophosphamide. With a median patient follow up of approximately four years from study entry, patients treated by the intraperitoneal route experienced a statistically significant improvement in survival (median: 49 months) compared to intravenous therapy (median: 41 months) \( p < 0.03 \).

In addition, women treated with intraperitoneal cisplatin experienced significantly less neutropenia and clinically relevant hearing loss. These findings are presumably due to lower peak levels of cisplatin achieved within the systemic compartment following intraperitoneal delivery, compared to intravenous administration.

This large, well-designed and well-conducted randomized study has provided strong support for the argument that high peritoneal cavity concentrations of an active cytotoxic agent can increase the effectiveness of treatment of women with small-volume residual advanced ovarian cancer. In addition, it demonstrates that this therapeutic strategy can be employed outside the tertiary research center with an acceptable degree of catheter-related side effects (e.g., infection, bowel perforation). However, it is important to note that the local toxicity of regional treatment will be dependent on the specific drug or drugs employed, and the favorable side-effect profile documented in this landmark study may not be observed with other cytotoxic drugs.

Unfortunately, this intergroup study was initiated 10 years ago, prior to the introduction of paclitaxel into the clinic and the demonstration of the impact of this agent on survival in advanced ovarian cancer. Thus, while this study has clearly shown the superiority of intraperitoneal cisplatin and intravenous cyclophosphamide (compared to intravenous cisplatin and cyclophosphamide) in small-volume residual advanced ovarian cancer, the impact of intraperitoneal cisplatin when combined with paclitaxel is unknown. This important question has been partially addressed by another recently completed intergroup study, but the results of this trial will not be available for several years.

However, for the present and based on available data, it is appropriate to conclude that the use of intraperitoneal cisplatin in combination with intravenous paclitaxel is a reasonable therapeutic strategy in women with small-volume residual advanced ovarian cancer (largest residual tumor masses ≤0.5-1 cm in maximum diameter) following tumor-debulking surgery.

**Intraperitoneal Paclitaxel**

With the demonstrated activity of paclitaxel in ovarian cancer, it was natural to examine this agent for intraperitoneal delivery [14]. Several additional factors suggested that paclitaxel might be a good candidate for regional therapy, including its large size and hepatic metabolism (increasing cavity exposure compared to the systemic compartment).

Two phase I trials have confirmed a major pharmacokinetic advantage (>1000-fold) for the peritoneal cavity compared to the systemic compartment following regional paclitaxel administration [11, 12]. In addition, potentially cytotoxic concentrations of the agent were found to persist within the cavity for more than a week following intraperitoneal treatment. These data suggest that with a weekly intraperitoneal paclitaxel dosing schedule it may be possible to continuously expose thin layers of tumor on the surface of the cavity to paclitaxel for the duration of treatment.

In theory, this strategy might be the “optimal” method for employing this cycle-specific agent against slowly dividing ovarian cancer cells [13]. In a phase II trial, the Gynecologic Oncology Group is currently examining a weekly intraperitoneal paclitaxel regimen as salvage treatment of women with small-volume persistent or recurrent ovarian cancer following initial systemic therapy. The results of this interesting trial should be available within the next year.
CONCLUSIONS

On the basis of what is currently known about the limitations and potential benefits of intraperitoneal therapy of ovarian cancer, in what clinical settings might investigators continue to explore potential roles for this unique therapeutic approach? Several suggested strategies and potential regimens in which to explore those areas are outlined in Table 5.

However, it always must be remembered that it is only through the conduct of well-designed and rigorously conducted clinical trials that the theory supporting regional drug delivery in the management of ovarian cancer can be translated into a strategy demonstrating a clinically meaningful impact on the long-term survival of women with this malignancy.

REFERENCES


Table 5. Reasonable clinical settings in which to explore a role for intraperitoneal therapy in the management of ovarian cancer

1. Initial treatment of small volume residual disease
   a. Intraperitoneal cisplatin + intravenous paclitaxel
   b. Intraperitoneal cisplatin + intraperitoneal paclitaxel
   c. Intraperitoneal cisplatin + intraperitoneal paclitaxel + intravenous paclitaxel;

2. Initial treatment of early stage, high-risk ovarian cancer (e.g., stage IC, stage II);

3. Consolidation following a negative second-look laparotomy/laparoscopy in patients with a high risk for recurrence (e.g., stage IIIC, grade 3 tumor); and

4. Salvage treatment of patients with microscopic (or very small volume macroscopic) disease at second-look laparotomy/laparoscopy with prior documented major response to initial systemic chemotherapy.