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# Intraperitoneal chemotherapy

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**Contents**



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## 1. Introduction

Interest in the direct intraperitoneal administration of antineoplastic agents as treatment for malignant disease principally confined to the peritoneal cavity began more than 40 years ago, with the introduction of cytotoxic alkylating agents into cancer medicine [1].

Since that time a great deal has been learned regarding the potential benefits and limitations of this therapeutic strategy.This article will briefly review the current status of intraperitoneal chemotherapy, with a particular focus on ovarian cancer, and briefly discuss future potential directions for clinical research in this area.

## 2. Rationale for intraperitoneal antineoplastic drug delivery

The basic aim of intraperitoneal chemotherapy is to expose cancer present within the peritoneal cavity to higher concentrations of drug for more prolonged time periods than possible with systemic drug delivery [2,3]. In theory, agents most appropriate for intraperitoneal administration would be those whose antineoplastic effects have been demonstrated to be enhanced (in either experimental models or actual clinical trials) either by increasing the duration or concentration of exposure to the malignant cells [4].

## 3. Phase 1: clinical trials of intraperitoneal therapy

A number of cytotoxic and biological agents have been investigated for their safety and pharmacokinetic advantage following intraperitoneal drug delivery (Table 1); [5].

### 3.1. Intraperitoneal cisplatin

The greatest experience with intraperitoneal chemotherapy has been with cisplatin, based on its central role in the management of ovarian cancer. Several phase 1 trials have confirmed a 10–20-fold pharmacokinetic advantage (both peak levels and area-under-the concentration (AUC) versus the time curve) associated with the intraperitoneal delivery of this drug, compared with its systemic administration [6–9].

Table 1
Pharmacokinetic advantage associated with intraperitoneal administration of selected antineoplastic agents

| Agent | Peak peritoneal cavity/plasma concentration ratio |
|---|---|
| Cisplatin | 20 |
| Carboplatin | 18 |
| 5-fluorouracil | 300 |
| Doxorubicin | 470 |
| Melphalan | 80 |
| Methotrexte | 90 |
| Paclitaxel | 1000 |

Table 2
Unique issues associated with intraperitoneal antineoplastic drug delivery

1. Local toxicity to peritoneal cavity (e.g. adhesion formation and subsequent bowel obstruction)
2. Adequacy of drug distribution
3. Establishment of safe, convenient, and cost-effective access to the peritoneal cavity
4. Adequacy of drug delivery to cancer by capillary flow
5. Limited penetration of agents directly into tumor tissue

In addition, there are minimal local side effects associated with intraperitoneal cisplatin treatment [6–9]. As a result, the dose limiting toxicities associated with regional delivery of cisplatin are the systemic effects of the agent (e.g. emesis, nephrotoxicity, neurotoxicity). This experience, along with formal pharmacokinetic analysis, reveals that the delivery of the cisplatin to tumor by capillary flow following intraperitoneal treatment is essentially equivalent to that achieved with intravenous delivery at maximally tolerated dose levels for the two routes of administration.

### 3.2. Intraperitonal paclitaxel

Of particular interest are recent data for the intraperitoneal administration of paclitaxel [10,11]. In addition to a pharmacokinetic advantage of three logs associated with its intraperitoneal delivery, cytotoxic concentrations of the agent have been demonstrated to persist within the peritoneal cavity for at least 7 days after a single treatment [11]. Therefore, at least in theory, with a weekly intraperitoneal paclitaxel treatment program, it is possible that at least the surface of the peritoneal lining will be continuously exposed to this cycle-specific cytotoxic agent.

## 4. Limitations of intraperitoneal antineoplastic therapy

Despite the potential clinical utility of intraperitoneal antineoplastic drug delivery, investigators in this clinical arena have long recognized a number of important practical and conceptual limitations associated with this therapeutic strategy. These issues are briefly outlined in Table 2.

### 4.1. Significance of 'relative' versus 'absolute' drug resistance

While it is possible to achieve extremely high drug

concentrations within the peritoneal cavity following regional delivery, clinical experience with this approach has clearly demonstrated that an agent which is inactive against a tumor at concentrations achievable following systemic therapy cannot be converted into an active agent simply by increasing the concentration of exposure [12–14]. Even a 10- or 100-fold increase in concentration will have little, if any, demonstrable impact on a tumor resistant to standard dose therapy.

However, as shown in multiple second-line intraperitoneal studies on ovarian cancer, a high surgically-documented objective response rate can be observed in individuals whose tumors have responded well to systemic therapy, but persist in small volumes (microscopic disease only or largest residual tumor nodule $< 0.5$ cm in maximal diameter) prior to the initiation of the intraperitoneal treatment strategy [12–16].

These data provide strong support for the concept that the higher drug concentrations achievable with intraperitoneal drug delivery may be beneficial in an individual patient demonstrating relative (i.e. major objective response but documented failure to eliminate the cancer), but not absolute (i.e. limited, minimal or no response to the prior systemic treatment program), resistance to a particular antineoplastic drug.

### *4.2. Importance of tumor volume*

Clinical experience has also clearly defined a second major limitation associated with the application of intraperitoneal antineoplastic drug delivery. While high concentrations of a number of agents have been documented within the peritoneal cavity following regional administration (Table 1), the actual depth of penetration of the drugs directly into the tumor is extremely limited.

Preclinical data involving several agents, including methotrexate [17], doxorubicin [18,19], 5-fluorouracil [20], and cisplatin [21], have revealed the ability of these drugs to penetrate into normal and tumor tissue will be only several cell layers to 1–3 mm from the peritoneal surface. Several clinical trials of second-line intraperitoneal chemotherapy in ovarian cancer have confirmed these experimental observations [12–16].

For example, in a retrospective analysis of such patients treated with a cisplatin-based intraperitoneal strategy at the Memorial Sloan–Kettering Cancer Center, a 32% surgically-confirmed complete response rate was achieved among the 50 individuals whose largest tumor nodule at the initiation of the second-line regimen was $< 1$ cm [12]. In contrast, the surgical complete response rate was only 5% for the 39 patients with a least a single tumor nodule $> 1$ cm in maximal diameter at the beginning of the intraperitoneal program.

Data for second-line single agent intraperitoneal paclitaxel as treatment for ovarian cancer provide further support for the importance of volume of residual disease at the initiation of regional treatment [15]. Of the 28 fully evaluable patients treated on a Gynecologic Oncology Group phase 2 trial who had only microscopic disease at the initiation of the second-line treatment program, 17 (61%) achieved a surgically-documented complete response. However, a complete response rate of only 3% was observed among the 31 individuals who had any residual macroscopic disease at the start of the second-line treatment program.

The striking difference between the objective response rates between microscopic and macroscopic disease demonstrated in the intraperitoneal paclitaxel trial is likely to be due to the fact that very limited concentrations of paclitaxel actually enter the systemic compartment following intraperitoneal administration. Thus, in contrast to the experience with intraperitoneal cisplatin where cytotoxic activity with regional delivery results from both direct penetration and systemic drug uptake [6–9,21], the activity of paclitaxel administered regionally must result from direct penetration into tumor tissue alone [10,11,15]. This experience strongly supports the hypothesis that the optimal strategy to employ intraperitoneal paclitaxel would be to combine regional delivery with systemic administration of the agent.

## 5. Randomized trials of intraperitoneal cisplatin as initial treatment of small volume residual advanced ovarian cancer

Despite the theoretical appeal of intraperitoneal therapy of ovarian cancer, and the interesting results observed during phase 2 trials (Table 3), the clinical utility of this therapeutic strategy remained in question in the absence of data from well-designed and conducted randomized phase 3 trials.

A particular difficulty in interpreting phase 2 trial data associated with intraperitoneal treatment was the fact that patients with small volume disease were dis-

Table 3
Agents demonstrating surgically-documented complete responses in phase 2 trials of second-line intraperitoneal therapy of ovarian cancer

| |
|---|
| Cisplatin |
| Carboplatin |
| Mitoxantrone |
| Paclitaxel |
| Interferon-alpha |
| Interferon-gamma |

covered (as discussed above) to be the only appropriate candidates for this approach. Therefore, if an apparent 'unexpectedly good outcome' was observed, for example in progression-free or overall survival, in a phase 2 trial, it was questioned whether these results simply reflected the natural history of disease in a particularly favorable subset of patients at this point in their malignancy [22–24].

### *5.1. Phase 3 trial: intraperitoneal cisplatin versus intravenous cisplatin as initial therapy of small volume residual advanced ovarian cancer*

The results of a randomized multi-institution phase 3 trial conducted in the United States involving more than 600 patients with 'small volume' residual ovarian cancer after initial surgical cytoreduction has been helpful in demonstrating a potential role for intraperitoneal cisplatin in this malignancy [25]. Patients participating in this trial, which was initiated in the mid 1980s, received cisplatin (100 mg/m$^2$), either via the intraperitoneal or intravenous routes. All patients also received intravenous cyclophosphamide.

While there were some toxicity differences between the two regimens (i.e. more abdominal discomfort and less neutropenia and tinnitus associated with intraperitoneal cisplatin), the major finding of this trial was a statistically significant improvement in overall survival associated with the regional cisplatin administration strategy. The median survival for individuals receiving intravenous cisplatin was 41 months, compared to 49 months for intraperitoneal cisplatin ($P = 0.02$).

### *5.2. Phase 3 trial: Intraperitoneal cisplatin versus intravenous cisplatin, both with intravenous paclitaxel as initial treatment of small volume residual advanced ovarian cancer*

Unfortunately, despite the findings of the large, well-designed and conducted multi-institutional study, intraperitoneal cisplatin has not been accepted by most investigators or clinicians as a standard initial chemotherapy option in small volume residual advanced ovarian cancer. While there are several possible explanations for this reluctance to embrace the results of the well-designed and conducted randomized trial noted above as sufficient justification for changing 'standard' clinical practice, the major explanation must be the absence of paclitaxel in either the control or experimental regimen.

Paclitaxel, which has been demonstrated to significantly improve the efficacy of therapy of ovarian cancer when combined with a platinum agent [26], was not a standard drug employed in ovarian cancer when the intraperitoneal study noted above was initiated. Thus, many clinicians question if the benefits associated with intraperitoneal cisplatin might be achieved simply by combining systemically delivered paclitaxel and a platinum agent.

A second multi-institution randomized trial, recently reported in abstract form only, has partially addressed this issue [27]. In this study, patients with small volume residual ovarian cancer following surgery received intravenous paclitaxel along with either intravenous or intraperitoneal cisplatin.

Patients treated on the experimental intraperitoneal arm of this trial also received two courses of moderately high dose carboplatin (AUC 9) prior to initiation of the intraperitoneal regimen. The hypothesis was that the two courses of carboplatin might be capable of 'chemically debulking' tumor to very small volume macroscopic or microscopic disease only prior to the initiation of the regional treatment program [28].

Unfortunately, these two carboplatin courses were found to be quite toxic to platelets, such that 20% of patients randomized to the experimental arm of this trial were only able to receive two or fewer courses of the subsequently scheduled intraperitoneal treatment. Despite the toxicity of this particular regimen, and the failure of a large percentage of individuals to take optimal theoretical advantage of the 10–20-fold greater cisplatin concentrations achievable with regional delivery, patients randomized to the experimental arm demonstrated a superior progression-free and overall survival, compared to the 'all intravenous' control arm.

The median progression-free survival for the intravenous and intraperitoneal regimens were 22.5 months and 27.6 months ($P = 0.02$, one tail), respectively [27]. Overall survival for the intravenous and intraperitoneal arms were 47.6 months and 52.9 months ($P = 0.056$, one tail), respectively.

### *5.3. Phase 3 trial: intraperitonal cisplatin and intraperitoneal paclitaxel with intravenous paclitaxel versus intravenous cisplatin and paclitaxel as initial treatment of small volume residual advanced ovarian cancer*

Difficulty interpreting the results of this second study, and the previously noted provocative data regarding the pharmacokinetic advantage associated with intraperitoneal paclitaxel, led the Gynecologic Oncology Group to initiate a third randomized intraperitoneal chemotherapy trial as initial therapy of small volume residual advanced ovarian cancer. Patients entered into the 'control arm' of this study receive the Gynecologic Oncology Group 'standard' of intravenous cisplatin and 24-h infusional paclitaxel [26]. Individuals on the experimental program receive intraperitoneal cisplatin and both intraperitoneal and intravenous paclitaxel. This study was recently activated and it will be

several years before even preliminary results are available.

For the present it is reasonable to conclude that the use of intraperitoneal therapy as initial treatment of ovarian cancer remains an attractive therapeutic approach for a subset of individuals with this malignancy. However, the overall impact of the strategy on survival of patients with ovarian cancer is uncertain, and an optimal intraperitoneal drug regimen in this clinical setting remains to be defined.

## 6. Intraperitoneal therapy as a 'consolidation strategy' in ovarian cancer

Despite the improved clinically- or surgically-defined complete response rate achieved in patients with advanced ovarian cancer treated with a systemic platinum/paclitaxel based chemotherapy regimen [26], the majority of individuals achieving this favorable state will ultimately relapse. In fact, for patients with high grade (grade 3) cancers found to have no evidence of disease at a second-look surgical assessment, the ultimate relapse rate is $\approx 50\%$ [29].

As individuals with advanced ovarian cancer who attain a surgical complete response have demonstrated major chemosensitivity to the initial treatment regimen, this may be the ideal setting in which to consider a 'dose intensive' intraperitoneal chemotherapy strategy. Assuming any undetected microscopic residual cancer is confined to the peritoneal cavity, the extremely high concentrations of drug in direct contact with the lining cells of the peritoneal cavity may be capable of producing an additional cytotoxic effect against cancer cells, beyond that achievable with concentrations previously reaching the malignancy by capillary flow.

The results of a single institution phase 2 trial of intraperitoneal cisplatin-based consolidation therapy in women achieving a surgically-documented complete response provides provocative support for this hypothesis [30]. Patients in this clinical state at the Memorial Sloan–Kettering Cancer Center were offered the option of receiving three courses of an intraperitoneal chemotherapy regimen (cisplatin plus etoposide), and were then followed for recurrence.

The Memorial investigators subsequently compared the outcome of this patient population with a non-randomized 'control group' treated at their institution who would have been eligible for the 'consolidation' intraperitoneal treatment strategy but did not enter the study. These second-look surgical procedures were performed by the same surgeons during an identical time period.

It must be noted that there are always serious concerns associated with a retrospective comparison of the survival of a 'treated population' to a non-randomized 'control population'. Extensive experience in the oncologic literature has demonstrated that the 'treated' population in many 'innovative experimental phase 2 trials' has superior baseline clinical characteristics compared with an unselected 'control population' (e.g. age, performance status, less co-morbid medical conditions, etc.).

However, in the comparative analysis conducted at Memorial there was evidence the 'selection bias' was actually in the opposite direction. The physicians at Memorial were apparently more likely to consider a patient for entry into the phase 2 intraperitoneal consolidation trial if they had a greater 'perceived risk' for developing recurrence.

As a result, only three of the 36 patients (8%) in the 'treated population' had initially presented with stage 2 disease, compared to 18 of 46 individuals (39%) in the 'control' population. In addition, 33% of the 'treated population' had their largest residual tumor nodule $>1$ cm in maximal diameter following initial surgical cytoreduction, and prior to the initiation of systemic chemotherapy, compared to only 20% of the 'control population'.

These data would strongly suggest the 'control population' should have experienced a lower inherent risk for the development of recurrence following the attainment of a surgically-documented complete response, or at least the same risk, compared to the 'treated population'.

However, the exact opposite was found. With a median follow-up of 36 months the relapse rate for the patients receiving intraperitoneal consolidation therapy was 39%, compared to 54% in individuals who did not undergo this strategy. For the 18 women who actually received all three planned courses of the intraperitoneal therapy, the relapse rate was only 28%.

While of interest, these data cannot substitute for randomized trials examining the role of intraperitoneal therapy as a consolidation strategy in advanced ovarian cancer. There have been two such multi-institution studies undertaken, one examining intraperitoneal cisplatin and the other intraperitoneal interferon-alpha. In both studies the control group did not receive any further therapy following documentation of a surgical complete response. It is hoped that the results of these important studies can provide information as to a potential role for intraperitoneal drug delivery in this clinical setting.

## 7. Intraperitoneal chemotherapy in the setting of persistent 'small volume' residual responsive ovarian cancer

While the majority of clinical experience employing intraperitoneal chemotherapy has actually been gener-

Table 4
Necessary conditions for consideration of second-line intraperitoneal chemotherapy as treatment of ovarian cancer

1. Evidence of major inherent chemosensitivity based on prior response to systemic platinum-based chemotherapy
2. Microscopic disease only or very small tumor nodules (<0.5 cm in maximum diameter) at initiation of intraperitoneal chemotherapy regimen
3. No or limited intraperitoneal adhesions

ated in this specific clinical setting [31], there remains no randomized controlled trial data to document the efficacy of this approach compared to alternative strategies.

However, in the absence of such definitive data, it is the opinion of this author that the use of intraperitoneal chemotherapy can be considered a reasonable therapeutic option in carefully selected patients meeting specific clinical criteria (Table 4).

Initially, there must be evidence of a major response to treatment, such that it is appropriate to label the cancer as 'highly chemosensitive'.

Then, the maximal volume of residual disease documented at the time of a second-look laparotomy or laparoscopy must be extremely limited. Microscopic disease only or very small tumor nodules ( < 0.5 cm in maximal tumor diameter) would be the only clinical settings where the use of intraperitoneal therapy has been suggested to result in a higher objective response rate than might be achieved with systemic drug treatment.

Finally, the patient must be an appropriate candidate for the specific technical requirements associated with this strategy. If there has been evidence of significant adhesions at prior surgeries, intraperitoneal treatment is not a reasonable option, in view of the inability to achieve adequate drug distribution.

As the majority of experience employing intraperitoneal treatment of small volume residual ovarian cancer has been with cisplatin, this would be the preferred agent in this clinical setting [31]. In addition, while no randomized comparative trials have been conducted, there are limited pre-clinical and clinical data available which support the superiority of intraperitoneal cisplatin over carboplatin in this clinical setting [32,33]. Therefore, patients considered for this approach must be able to tolerate the potential toxicity of cisplatin delivered in the second-line treatment setting.

## 8. Intraperitoneal therapy of peritoneal mesothelioma

Peritoneal mesothelioma is an uncommon malignancy for which there has been limited clinical experience employing intraperitoneal chemotherapy. Several institutions have evaluated intraperitoneal cisplatin, either as a single agent [34,35], or in combination with mitomycin [36,37], or doxorubicin and whole abdominal radiation therapy [38,39]. Subjective responses, including control of malignant ascites and prolonged disease-free survival have been reported in these small series.

While it is difficult to draw any major conclusions from this limited experience, it is at least possible to suggest patients who might or might not be reasonable candidates to consider for this therapeutic strategy, based on the previously reported observations in mesothelioma, and the more extensive experience with intraperitoneal chemotherapy of ovarian cancer.

Individuals with this malignancy who present with large volume disease which cannot be resected to leave the patient with microscopic disease only or very small volume macroscopic cancer ( < 0.5 cm in maximal diameter) within the peritoneal cavity prior to intraperitoneal drug delivery would not be good candidates for this therapeutic strategy.

As with ovarian cancer, the known depth of penetration of cytotoxic agents strongly argues against treating patients with large tumor bulk. In addition, while ascites may be decreased following intraperitoneal treatment in this clinical setting, available data do not support the conclusion that this approach has a greater opportunity to produce a favorable symptomatic response compared to systemic delivery of a platinum-based chemotherapy regimen.

In contrast, for patients with 'small volume' peritoneal mesothelioma, documented either prior to or following surgical tumor debulking, regional therapy has some appeal. However, the limited information available regarding the potential clinical efficacy of surgical cytoreduction and intraperitoneal chemotherapy in the setting, must be explained in detail to the patient before embarking on this aggressive and potentially morbid therapeutic strategy.

## 9. Intraperitoneal therapy of gastrointestinal cancers

The intraperitoneal administration of cytotoxic agents as therapy of gastrointestinal malignancies has also been examined in a small number of clinical trials [40]. Several concerns with intraperitoneal treatment make this group of cancers a less attractive clinical setting for applying this approach than is the case with ovarian cancer.

First, there is no 'platinum equivalent' in gastrointestinal malignancies, a single agent with major activity which might be enhanced by increasing its dose intensity. Second, the pattern of spread of gastrointestinal cancers is much more likely to involve the liver and regional lymph nodes, areas which will not be favorably

influenced by higher drug concentrations within the peritoneal cavity.

Finally, surgical cytoreduction of metastatic implants is not a standard treatment strategy in the management of gastrointestinal cancers. There is no evidence based on a critical review of the oncologic literature to suggest the use of intraperitoneal chemotherapy following surgical cytoreduction of metastatic gastrointestinal cancers results in a favorable clinical outcome. Reports to the contrary suggesting prolonged survival of a subset of such patients (e.g. pseudomyxoma peritonei) treated with aggressive surgery and intraperitoneal chemotherapy likely represent the natural history of these slow growing cancers and the benefits associated with surgical tumor debulking alone [41].

Thus, the most appropriate setting in which to examine intraperitoneal cytotoxic drug delivery as a treatment strategy for gastrointestinal cancers would be as adjuvant therapy following initial surgery in individuals with a high risk for the development of peritoneal cavity recurrence [40,42]. Assessment of this approach will require the conduct of well-designed and conducted large scale randomized trials [43,44].

It will also require agreement among clinical investigators as to the drug(s) and treatment schedules to be examined in such studies. No such agreement or consensus currently exists. Therefore, it is uncertain if, and when, large scale appropriately controlled randomized trials of adjuvant intraperitoneal chemotherapy will be conducted in this clinical setting. Until such studies are performed, intraperitoneal chemotherapy for gastrointestinal cancers should only be employed as a component of well-designed clinical trials.

## 10. Conclusions

Despite the relatively long history of investigation of intraperitoneal chemotherapy, few randomized studies have been conducted to document the clinical utility of this approach, compared to systemic therapy. However, where these studies have been undertaken in patients with ovarian cancer they have revealed a small, reproducible, and statistically significant, favorable impact on progression-free and overall survival.

Further studies are needed to define where it is reasonable to consider intraperitoneal anticancer drug delivery to be a 'standard treatment option' in the management of cancers principally confined to the peritoneal cavity.

## Reviewers

This paper was reviewed by David S. Alberts, M.D., Professor of Medicine and Pharmacology, Director, Cancer Prevention and Control, Associate Dean for Research, College of Medicine, Acting chief, Section of Hematology and Oncology, Arizona Cancer Center, College of Medicine, 1515 North Campbell Avenue, P.O. Box245024, Tuscon, AZ 85724-5024 and Richard R Barakat, M.D., Division of Gynecologic Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, NY 10021, and Franco M. Muggia, M.D., New York University Medical Center, Kaplan Comprehensive Cancer Center, 550 First Avenue, NY 10016.

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## Biography

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