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Intraperitoneal Drug Delivery of Antineoplastics

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Contents

Abstract

The administration of antineoplastic agents directly into the peritoneal cavity as treatment of localised cancer is based on sound pharmacokinetic principles. This unique technique has to the potential to optimise outcome in settings where preclinical and clinical data suggest that cytotoxicity of a specific drug against a particular tumour type is enhanced by either increasing the drug concentration or duration of exposure.

Phase I trials have confirmed the safety and pharmacokinetic advantage for a number of agents delivered by the intraperitoneal relative to the systemic route, including cisplatin (10- to 20-fold advantage for regional delivery), carboplatin (10- to 20-fold advantage), and paclitaxel (1000-fold advantage). In phase II trials, performed mostly in patients with ovarian cancer, this approach has achieved objective responses in settings where intravenous drug delivery has not achieved the desired effect (e.g. surgically documented complete response using intraperitoneal cisplatin as second-line therapy of ovarian cancer). Phase III trials employing intraperitoneal cisplatin as initial treatment of small volume advanced ovarian cancer have demonstrated that regional therapy results in a modest, but statistically significant, improvement in both progression-free and overall survival compared to intravenous cisplatin.

Further exploration of this novel method of treatment, including the conduct of definitive randomised phase III clinical trials, is indicated in ovarian cancer and in other tumour types where clinical manifestations are principally localised to the peritoneal cavity.

The intraperitoneal delivery of antineoplastic agents as a management strategy for malignant disease principally confined to the peritoneal cavity has been explored for more than 4 decades.[1] Fortunately, over the past 10 years, data have become available to define patient populations likely to be reasonable candidates for regional treatment. In addition, the results of randomised, controlled clinical trials have provided the first evidence that intraperitoneal chemotherapy may have a significant impact on both progression-free and overall survival in ovarian cancer.

This review briefly highlights the rationale for intraperitoneal drug delivery, presents data from a limited number of phase II trials which help to define future directions for intraperitoneal treatment, and discusses the results of randomised trials employing regional chemotherapy in the management of ovarian and gastrointestinal cancers.

1. Rationale for Intraperitoneal Antineoplastic Therapy

The basic goal of intraperitoneal antineoplastic drug delivery is to expose cancer present within the peritoneal cavity to higher concentrations of drug for longer periods of time than is possible with systemic treatment.[2] The antineoplastic activity of some agents against specific cancers has been demonstrated to be enhanced, either in clinical studies or experimental systems, by increasing the concentration or duration of exposure. For these drugs, intraperitoneal delivery has the theoretical potential to improve the extent of tumour cell kill.[3]

Several features of antineoplastic drugs favour intraperitoneal delivery (table I).[2,4,5] While an antineoplastic agent need not have all of these properties to be useful after intraperitoneal administration, selecting a drug which most closely fits the profile of the 'ideal agent' will enhance the chances of developing an effective therapeutic strategy.

Intraperitoneal drug delivery may be a rational approach against:

(i) tumours principally confined to the abdominal cavity for most of their natural history

(ii) tumours where intraperitoneal spread (rather than metastases to regional lymph nodes or the systemic compartment) is the major route of disease progression, and

(iii) tumours known to be responsive to effective and available antineoplastic drugs.

On the basis of these considerations, there can be little argument that ovarian cancer is ideally suited to intraperitoneal drug delivery, and most clinical trials evaluating intraperitoneal therapy have been conducted in individuals with this tumour type.

Table I. Features of antineoplastic agents favouring intraperitoneal delivery in the management of malignant disease

1. Demonstrated activity against the specific tumour type
2. Evidence (in clinical trials or preclinical models) of enhanced cytotoxicity against the tumour associated with an increase in either drug concentration or duration of exposure
3. Known hepatic metabolism to non-toxic metabolite(s) (intraperitoneally administered drugs enter the portal circulation before entering the systemic compartment)
4. Water soluble (slower exit from the peritoneal cavity)
5. High molecular weight (slower exit from the peritoneal cavity)
6. Not a vesicant (reduces local toxicity to the peritoneal lining)

2. Phase I Trials

A number of cytotoxic and biological agents have been examined for their safety and potentially advantageous pharmacokinetic properties following intraperitoneal delivery (table II).[4] The pharmacokinetic advantage for peritoneal cavity exposure [expressed as the ratio of either peak drug peritoneal concentration or area under the peritoneal concentration versus time curve (AUC) relative to the systemic concentration] for selected agents has ranged from 20-fold, for cisplatin and carboplatin,[6-9] to as high as 1000-fold, for paclitaxel.[10,11]

For a number of drugs (e.g. doxorubicin,[12] mitoxantrone,[13] mitomycin[14] and paclitaxel[10,11]) examined for possible use as intraperitoneal therapy, the dose-limiting toxicity is abdominal pain from direct peritoneal irritation. For other agents, including cisplatin and carboplatin,[6-9] local adverse effects are minimal in most patients after in-

traperitoneal administration. Thus, for these latter drugs, the intraperitoneal concentration can be escalated until systemic toxic effects (e.g. bone marrow suppression) become the dose-limiting factor.

These findings have important clinical implications. For example, at the maximally tolerated dose of intraperitoneal cisplatin, as much of the agent will reach the systemic compartment (and tumour by subsequent capillary flow) as if the drug had been delivered systemically. That is, with the same degree of systemic toxicity there will almost certainly be the same degree of tumour exposure to the drug through systemic blood flow. In fact, pharmacokinetic studies have confirmed that systemic cisplatin concentrations are similar after intraperitoneal or intravenous delivery.

In contrast, after intraperitoneal paclitaxel administration systemic exposure is less than after intravenous administration at the maximally tolerated dose. Thus, to achieve optimal tumour exposure to this agent it may be necessary to deliver the drug both systemically and regionally.

3. Phase II Trials

As noted in section 1, most intraperitoneal antineoplastic drug trials conducted over the past 10 to 15 years have focused on ovarian cancer, with cisplatin being the cornerstone for many of these studies. Cisplatin was an excellent agent to employ in these phase II efficacy studies for several reasons.

Table II. Pharmacokinetic advantage for selected antineoplastic agents when administered by the intraperitoneal route

Agent	Ratio of peak peritoneal cavity concentration/peak systemic circulation concentration
Cisplatin	20
Carboplatin	18
Doxorubicin	470
Melphalan	80
Paclitaxel	1000
Methotrexate	90
Fluorouracil	300

Firstly, this class of drugs has clearly been shown to be the most active in the treatment of ovarian cancer.[15] Secondly, previously reported phase I studies confirmed both the safety and pharmacokinetic advantage (20-fold ratio) associated with the intraperitoneal administration of the agent.[6-9] Finally, as noted in section 2, regional delivery of cisplatin was shown to not compromise systemic exposure to the drug.

A number of phase II studies documented the ability of intraperitoneal cisplatin to produce objective antineoplastic responses when used as second-line treatment of women with advanced ovarian cancer.[4,5] In several series, approximately 20 to 40% of patients with small volume residual ovarian cancer at the completion of front-line chemotherapy (documented at second-look laparotomy) achieved a surgically-defined complete response following intraperitoneal cisplatin (confirmed at the performance of a third-look surgical evaluation).

Subsequent retrospective analysis of a number of these second-line chemotherapy trials has revealed several important clinical features which appear to be useful in predicting a favourable response to the intraperitoneal delivery.[16-18]

Firstly, individuals with the smallest volume of disease at the initiation of intraperitoneal therapy achieved the highest (surgically-documented) objective response rate. This included individuals with microscopic disease only, or those with only minimal macroscopic disease (largest tumour nodules < 0.5cm in maximal diameter).

This finding should not come as a surprise, as earlier preclinical data have documented that the actual depth of direct penetration of antineoplastic agents into normal or malignant tissue following regional delivery is very limited, i.e. from multiple cell layers to a maximum of perhaps 1 millimetre from the peritoneal surface.[19-23] Thus, the high local drug concentrations associated with intraperitoneal drug administration (10- to 1000-fold greater than achieved in the tumour through drug

delivered by capillary flow) will probably only be clinically relevant for very thin layers of tumour on the peritoneal surface.

Secondly, individuals receiving intraperitoneal cisplatin with small volume disease at the initiation of the second-line regimen who had failed to demonstrate objective evidence of tumour regression after previous systemic chemotherapy did not exhibit a response to the regional treatment programme (surgical complete response rate <10%).[16-18] This finding was in sharp contrast to what was observed in women who had achieved at least a partial response to initial therapy, but who had persistent microscopic or small volume residual macroscopic disease at the time of a second-look laparotomy (surgical complete response rate 30 to 40%).

This experience strongly supports the concept that antineoplastic agents in concentrations achievable within the peritoneal cavity following regional therapy can overcome relative, but not absolute, drug resistance. If an individual tumour has not responded to systemic therapy, even 10-fold or higher increases in drug concentration will not have a clinically relevant impact on further tumour cell kill.

Intraperitoneal paclitaxel has also been examined in a multicentre phase II trial as a treatment strategy for women with persistent ovarian cancer following initial chemotherapy.[24] A high surgically-documented response rate was demonstrated in this study. However, these responses were observed only in patients with microscopic disease (complete response rate: 60%). Patients with any macroscopic residual cancer at the initiation of intraperitoneal drug delivery experienced a much lower surgically-defined complete response rate (<10%). These data support previously noted preclinical and clinical data suggesting the limited depth of penetration of this large molecular weight drug, and the known low level of systemic exposure to paclitaxel following regional delivery.[10,11]

Several biological agents, including interferon (IFN)-α,[25] IFN-γ,[26] and interleukin-2,[27] have been examined for intraperitoneal administration in the phase II setting as therapy of persistent small volume residual ovarian cancer following initial systemic chemotherapy. Objective responses (including surgically-defined complete responses) and prolonged survival for a subset of patients treated in this manner have been observed.

Phase II trials using regional antineoplastic drug delivery have been conducted in patients with other malignancies involving the peritoneal cavity, including gastric and colon cancer,[28] peritoneal mesothelioma,[29,30] and pseudomyxoma peritonei.[31] Unfortunately, in contrast to ovarian cancer, there are several major limitations to the development of an effective regional therapy strategy in these clinical settings.

Such limitations include the lack of highly effective antineoplastic agents in these malignancies (for example, compared to cisplatin in ovarian cancer) and patterns of tumour progression other than direct peritoneal spread.

In addition, the natural history of disease in some patients with these tumour types (e.g. pseudomyxoma peritonei from a low grade carcinoma of the appendix) can be highly heterogeneous, and surgical resection alone may be a reasonably effective palliative approach. In this setting it remains unclear what role regional antineoplastic drug therapy may play in standard patient management.

Despite these concerns, if future drug development programmes in these malignancies identify effective antineoplastic agents with properties appropriate for intraperitoneal delivery, additional investigations into regional delivery clearly will be justified.

4. Impact on Survival

Despite the theoretical appeal of regional antineoplastic drug delivery in certain clinical settings, until relatively recently there remained no data from well-designed, randomised phase III trials to demonstrate a favourable impact of such therapy on survival.

In the case of ovarian cancer, long term evaluation of patients treated with cisplatin-based second-line intraperitoneal therapy in several phase II

trials suggested the potential for prolonged survival.[32-34] However, it remained unclear whether this outcome resulted from a direct influence of the regional therapeutic strategy, or simply reflected the well recognised (but poorly understood) favourable natural history of disease in a subset of women with persistent or recurrent ovarian cancer following initial systemic chemotherapy.

For example, one of the most provocative reports of the clinical use of intraperitoneal cisplatin was provided by investigators from the Memorial Sloan-Kettering Cancer Center (New York, NY, USA).[35] In a phase II trial conducted over several years, patients with advanced ovarian cancer (stages 2 to 4) who achieved a surgically-documented complete response to initial systemic chemotherapy were offered treatment with a 'consolidation chemotherapy programme'. This included 3 courses of cisplatin-based intraperitoneal chemotherapy. The authors subsequently compared the recurrence rate in this patient population with the rate in a concurrent (not randomised) group of patients treated at their institution during the same time period by the same surgeons, but who did not receive the intraperitoneal consolidation strategy.

In their analysis, the investigators demonstrated that the control population (no consolidation treatment) would have been predicted to be at a lower risk for the subsequent development of recurrence based on known clinical features of disease (e.g. fewer patients with suboptimal stage 3 disease at the initiation of systemic chemotherapy), compared with the women treated with the consolidation strategy. However, there was a statistically significant ($p = 0.03$) reduced risk of recurrence in the individuals who received the regional therapy approach.[35]

Unfortunately, while these data are of interest, they cannot replace the results of well-designed randomised trials undertaken without recognised or unrecognised patient selection bias.

5. Phase III Trials

5.1 Ovarian Cancer

The publication of a landmark paper in 1996[36] for the first time demonstrated that regional therapy of ovarian cancer had the potential to have a major impact on survival. In this study, involving >600 women with small volume advanced ovarian cancer, patients were randomised to receive either intravenous or intraperitoneal cisplatin 100 mg/m^2. All individuals participating in this trial also received intravenous cyclophosphamide 600 mg/m^2.

As anticipated, more patients had abdominal discomfort in the group receiving the regional treatment programme, although few discontinued therapy because of this adverse effect. Of note, there was a statistically significant reduction in both neutropenia and ototoxicity associated with the intraperitoneal rather than the intravenous route of drug delivery.

However, of greatest importance, there was a statistically significant improvement in median overall survival associated with intraperitoneal cisplatin therapy (49 *vs* 41 months, $p = 0.02$). The relative reduction in the risk of death was approximately 22%, comparable to the benefits achieved with the use of adjuvant tamoxifen therapy for women with node-positive breast cancer.[37]

Unfortunately, this randomised study was initiated before the important role played by paclitaxel in the management of advanced ovarian cancer became apparent.[38] Therefore, it remained unknown whether intraperitoneal therapy provided an advantage relative to the substitution of paclitaxel for cyclophosphamide in the treatment of small volume residual advanced disease.

However, a report of a second multicentre, randomised trial[39] has provided further evidence that intraperitoneal delivery of cisplatin may increase survival, even when systemic paclitaxel is included in the treatment programme.

In this study, patients received either systemically delivered cisplatin and paclitaxel or an experimental programme of 2 courses of moderately

high dose carboplatin (AUC 9) followed by intraperitoneal cisplatin and intravenous paclitaxel.[39] The initial 2 carboplatin cycles were administered in an effort to 'chemically debulk' the tumour, prior to intraperitoneal drug delivery, to optimise the effect of high local drug concentrations associated with regional treatment.[40]

Patients randomised to the experimental arm of this study experienced a 19% reduction in the risk of death, an outcome strikingly similar to results of the previously noted randomised phase III intraperitoneal cisplatin trial.[36] Both progression-free survival (28 *vs* 22 months, $p = 0.01$) and overall survival (63 *vs* 52 months, $p = 0.05$) were improved in the experimental therapy arm. Of note, survival was increased in the intraperitoneal arm even though 20% of these patients received ≤2 courses of the regional therapy. Treatment was withheld principally because of excessive thrombocytopenia associated with the 2 high-dose carboplatin cycles.[39]

Based on the results of these 2 well-designed and -conducted multicentre phase III trials, and the favourable pharmacokinetics and clinical results associated with intraperitoneal paclitaxel delivery, the Gynecologic Oncology Group initiated a third randomised trial of regional therapy. This trial examined a regimen of intravenous cisplatin and paclitaxel compared with an experimental programme of intraperitoneal cisplatin plus both intraperitoneal and intravenous paclitaxel. The results of this study, which should be available within the next several years, are awaited with interest.

5.2 Other Types of Cancer

To date, there have been few randomised trials of intraperitoneal therapy in other tumour types. In a study conducted at the National Cancer Institute (Bethesda, Maryland, USA), patients with localised colon cancer and a high risk of recurrence were randomised to receive adjuvant therapy with either systemic or intraperitoneal fluorouracil.[41] Although the overall survival was not different in the 2 study arms, patients receiving local therapy had a lower incidence of peritoneal cavity recurrence. These results support the concept that high local concentrations of fluorouracil can influence tumour growth. However, the limited overall activity of the agent, as well as direct tumour spread to the liver (through the portal circulation) and regional lymph nodes, prevents this measurable regional effect from being translated into genuine clinical benefit.

In another randomised trial, investigators in Japan examined the intraperitoneal administration of carbon-absorbed mitomycin as an adjuvant strategy in patients with gastric cancer.[42] Compared with an untreated control population (surgical treatment only), individuals receiving intraperitoneal mitomycin showed superior responses (statistically significant difference; $p < 0.01$). Unfortunately, a second trial conducted in Austria which examined this novel treatment strategy failed to confirm a favourable impact on survival and noted a significant incidence of postoperative complications with the local approach.[43]

However, results of a third trial examining early postoperative intraperitoneal mitomycin and fluorouracil delivered following resection of gastric cancer (stage II or III) suggest a survival advantage for the subset of individuals with stage III disease receiving the regional treatment programme.[44] These results require confirmation.

6. Future Directions

While the basic principles and limitations of the intraperitoneal administration of antineoplastic agents are reasonably well established, few definitive randomised trials have been conducted to critically define a role for this unique treatment strategy in standard clinical practice. Settings where intraperitoneal antineoplastic drug delivery is a rational therapeutic option are outlined in table III.

It must be emphasised that while preclinical data, anatomical considerations, and the results of limited phase II trials may provide strong support for a role for intraperitoneal therapy in patient management, none of the settings suggested for regional treatment (table III) can be considered

Table III. Clinical settings where intraperitoneal antineoplastic drug administration is a rational management strategy

1. Initial chemotherapy of small volume residual advanced (stage 3) ovarian cancer (e.g. microscopic or largest residual macroscopic tumour <1cm in maximum diameter following initial surgical cytoreduction) (supported by results of randomised trials)
2. Initial chemotherapy of 'early stage' ovarian cancer with a high risk for disease recurrence (e.g. stage 1, grade 3 disease)
3. Consolidation therapy of advanced ovarian cancer following a negative second-look laparotomy
4. Second-line chemotherapy of ovarian cancer in the presence of microscopic or very small volume residual macroscopic disease (maximum tumour diameter <0.5cm) in patients with a documented response to initial systemic chemotherapy
5. Adjuvant chemotherapy of gastric cancer
6. Adjuvant therapy of colon cancer with high risk of recurrence
7. Initial chemotherapy of peritoneal mesothelioma following surgical resection of all gross residual disease or with persistent very small volume residual macroscopic disease (maximum tumour diameter <0.5cm)

'standard-of-care' in the absence of data from well-designed and -conducted randomised clinical trials.

In the case of ovarian cancer, it is important to explore further the use of carboplatin- rather than cisplatin-based intraperitoneal therapy, because of the former's superior systemic toxicity profile. While preclinical data,[45] and a small retrospective analysis of the results of nonrandomised phase II trials,[46] have suggested the intratumour concentrations of carboplatin following intraperitoneal delivery may be somewhat inferior to cisplatin, comparative trials have not been conducted.

However, it is reasonable to speculate that oncologists will be less likely to consider, and patients will be less willing to receive, therapy associated with greater systemic toxicity, even if a definite (but modest) increase in progression-free and overall survival is gained. Thus, it will be important to determine if the survival benefit with intraperitoneal cisplatin administration in patients with small volume residual advanced ovarian cancer can be achieved with carboplatin, with its anticipated reduction in treatment-related emesis, nephrotoxicity and neurotoxicity.

Finally, it is also possible that the clinical utility of the intraperitoneal delivery of cytotoxic agents may be improved though attention to important technical limitations of the procedure. For example, preclinical modelling has suggested that, while increased penetration of drugs directly into tumour tissue will be difficult to achieve, methods to improve mixing within the peritoneal cavity may enhance antineoplastic efficacy.[47]

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