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Intraperitoneal Therapy in the Management of Ovarian Carcinoma

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The intraperitoneal administration of chemotherapeutic and biological agents as therapy of ovarian carcinoma is based on both theoretical considerations and experimental evaluations which suggest that tumor present in the cavity can be exposed to higher concentrations of certain antineoplastic drugs than can be accomplished if the agents are administered systemically. Recent clinical data have confirmed both the safety and pharmacokinetic advantage associated with this approach. Surgically defined responses have been observed in patients with small-volume residual refractory ovarian carcinoma treated with several single-agent and combination intraperitoneal therapeutic programs. While significant activity has been noted in this clinical setting, a clearly defined role for intraperitoneal treatment in the standard management of ovarian carcinoma remains to be determined.

The intraperitoneal administration of chemotherapeutic agents in the management of ovarian carcinoma began in the 1950s with the introduction of nitrogen mustard as an antineoplastic drug [1,2]. Unfortunately, the intraperitoneal instillation of the early alkylating agents, while occassionally resulting in impressive control of malignant ascites formation, was also associated with considerable local toxicity. In addition, objective anti-tumor responses were rarely observed. Thus, intraperitoneal therapy became relegated to those situations where it was desired to provide only temporary control of ascites formation to improve the quality of the patient's life when all other therapeutic options were eliminated.

It was not until the late 1970s that interest was renewed in the concept of employing intraperitoneal chemotherapy as a therapeutic approach to treat tumors confined to the peritoneal cavity. This renewed interest was based on the publication of a mathematical model, developed by investigators at the National Cancer Institute, which suggested that exposure of tumors in the peritoneal cavity to concentrations of cytotoxic agents instilled directly into the cavity would far exceed the level of exposure achieved following systemic drug administration [3,4].

A number of important principles supporting and limiting the clinical use of intraperitoneal chemotherapy have been defined in pre-clinical studies conducted at

Abbreviations: CR: complete response 5-FU: 5-fluorouracil PR: partial response

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several centers[5]. These basic principles are presented below in outline form:

1. Agents most suitable for intraperitoneal administration are those which slowly exit the peritoneal cavity following intraperitoneal administration and which are rapidly cleared from the systemic circulation upon entry into that compartment. These properties maximize cavity exposure to the agent while minimizing systemic exposure and the potential for systemic toxicity [3,4].
2. Agents which are rapidly and extensively metabolized into non-toxic metabolites during their first passage through the liver are particularly attractive for intraperitoneal administration, as uptake of drugs from the peritoneal cavity is largely via the portal circulation [6,7].
3. Penetration of chemotherapeutic agents directly into tumor tissue is limited to a depth of several cell layers to several millimeters [5,8–12]. This fact would strongly suggest that any benefit to be gained from intraperitoneal chemotherapy would be limited to those situations where only *very small tumor volume* remains in the cavity, either following surgical debulking alone or debulking surgery plus systemic chemotherapy.
4. As any benefit to be gained from intraperitoneal chemotherapy (over that accomplished with systemic drug administration) would rely on *free surface diffusion* of the agent in *direct contact* with tumor tissue, it is critical that the drug reach all regions of the cavity following instillation. Large treatment volumes ($\geq$2 liters) appear to optimize drug distribution [13–15]. Unfortunately, for several reasons, including both surgery- and chemotherapy-induced adhesion formation, it cannot be assumed that all patients will achieve adequate distribution of drug-containing fluid following intraperitoneal treatment.
5. One major theoretical concern associated with the intraperitoneal instillation of antineoplastic agents is that drug delivery to tumor by *capillary flow* (the mechanism by which the drug reaches the tumor following systemic administration) will be diminished. Thus, it is argued, even if local exposure is increased, overall exposure of the tumor to the antineoplastic agent may be reduced. If cytotoxic drugs which are *not* locally toxic to the peritoneal lining are selected for intraperitoneal therapy, it is possible to escalate the amount of drug delivered to the point where dose-limiting toxicity will be the systemic side effects of the agent [5]. In such a situation, exposure of the plasma (and, ultimately, the tumor by capillary flow) to the antineoplastic agent following intraperitoneal administration will equal that accomplished following systemic drug delivery. Thus, an important goal in designing intraperitoneal treatment programs should be to select agents which do not produce such severe local toxicity that systemic exposure is compromised. If, however, drugs are employed which are limited by local toxic effects, it must be understood that systemic exposure to the agent(s) will be diminished compared to that achieved with intravenous delivery.
6. Finally, a number of investigators have explored various options for delivering intraperitoneal therapy in a safe and convenient manner [5,16]. While percutaneous catheter placement with each treatment course is certainly an option [17], there is genuine concern that bowel perforation may result, particularly in individuals without ascites and those who have undergone one or more previous laparotomies with subsequent adhesion formation [18].

TABLE 1
Chemotherapeutic Agents Examined for Their Safety, Pharmacokinetic Advantage, and Possible Efficacy in Ovarian Carcinoma

Cisplatin
Carboplatin
5-fluorouracil
Doxorubicin
Mitoxantrone
Melphalan
Mitomycin-C
Methotrexate
Cytarabine
Etoposide

Surgically implanted catheters (the Tenckhoff type) reduce the risk of this complication of therapy [19–21]. When these implanted catheters are attached to subcutaneous delivery devices, patient acceptance of the catheter improves and the incidence of catheter-related infections, the major problem associated with these devices, appears to decrease [18,21].

SINGLE-AGENT TRIALS OF INTRAPERITONEAL CHEMOTHERAPY IN OVARIAN CARCINOMA

A number of chemotherapeutic agents have been examined for their safety, pharmacokinetic advantage, and efficacy when delivered by the intraperitoneal route in the treatment of ovarian carcinoma (Table 1) [5]. Table 2 presents the pharmacokinetic advantage associated with selected agents when administered by the intraperitoneal route.

In the following section, the results of phase I and phase II trials examining a potential role for single-agent intraperitoneal chemotherapy in the management of ovarian carcinoma will be briefly summarized.

Cisplatin

Due to its central place in the management of ovarian carcinoma, it is logical that cisplatin would be one of the first drugs to be examined for intraperitoneal administration [22]. A number of phase I and phase II trials employing this agent in the management of refractory ovarian carcinoma have been reported [12,15,23–27]. The results of these trials are outlined in Table 3. A reasonable dose of cisplatin administered as a single agent by the intraperitoneal route is 100 mg/m^2.

It is important to note that there is a strong experimental basis to support the intraperitoneal use of cisplatin in refractory ovarian carcinoma. Several investigators have noted that, under experimental conditions, it is difficult to make human ovarian carcinoma cells more than two to five times resistant to cisplatin either *in vitro* or *in vivo* [28]. In theory this finding means that if it were possible to expose a tumor to somewhat higher concentrations of cisplatin (i.e., eight to ten times higher doses than the standard used in initial treatment regimens) it is conceivable that clinical resistance to cisplatin might be overcome.

TABLE 2
Pharmacokinetic Advantage Associated with the Intraperitoneal Administration of Selected Antineoplastic Drugs

Agent	Mean Peak Peritoneal Cavity/Plasma Concentration Ratio
Cisplatin	20
Carboplatin	18
5-FU	298
Doxorubicin	474
Mitoxantrone	620
Melphalan	93
Mitomycin-C	71

Unfortunately, it is not possible to significantly increase the dose of systemically delivered cisplatin to patients beyond that which is the standard used (100–120 mg/m^2) due to the development of severe side effects—principally neurotoxicity [22]. As noted in Table 3, however, following intraperitoneal administration, the exposure of the peritoneal cavity to the agent is approximately 10 to 20 times greater than that of the systemic circulation. Thus, at least in those situations where residual ovarian carcinoma is present in only very small volumes following cisplatin-based systemic therapy (microscopic disease only or tumor nodules ≤ 0.5 cm), it might be possible to kill a major portion of the remaining tumor by using the same agent delivered by the intraperitoneal route. An interesting approach has been examined at the University of California, San Diego, utilizing intraperitoneal cisplatin and a systemically delivered neutralizing agent for the cytotoxic drug (sodium thiosulfate) [15]. This group has demonstrated that single-agent cisplatin can be administered intraperitoneally up to doses of 270 mg/m^2 with acceptable systemic toxicity.

Carboplatin

Compared to cisplatin, there has been far less experience using carboplatin administered by the intraperitoneal route. In several phase I trials, this agent has been shown to produce limited or no local toxicity and to possess a pharmacokinetic advantage which approximates that found with cisplatin [29–31]. Not surprisingly, dose-limiting toxicity has been bone marrow suppression, principally thrombocytope-

TABLE 3
Summary of Phase I–II Trials Employing Intraperitoneal Cisplatin in Refractory Ovarian Carcinoma

Pharmacokinetic advantage: 10- to 20-fold increased exposure of the peritoneal cavity following intraperitoneal delivery as compared to the systemic circulation
Dose-limiting toxicity: Systemic effects of the agent
Local toxicity: Minimal or no abdominal pain following intraperitoneal instillation
Surgical findings: Mild to moderate "filmy" adhesions noted
Long-term complications: To date, none appreciated
Efficacy: 30–50 percent of patients with "small-volume" refractory ovarian carcinoma will experience a surgically documented response (CR or PR)

CR, complete response
PR, partial response

nia. Surgically defined responses, including complete responses in patients with small-volume residual ovarian carcinoma, have been observed. The reported trials have demonstrated that carboplatin can be safely administered by the intraperitoneal route as a single agent at a dose of approximately 300 mg/m^2. In patients with mild to moderate compromise of renal function (creatinine clearance 30–60 ml/minute) the dose of carboplatin should be reduced to 200–250 mg/m^2.

5-Fluorouracil (5-FU)

5-FU was one of the first drugs to be examined for a role following intraperitoneal delivery because it was known that the agent is rapidly metabolized during its first passage through the liver [32]. As 5-FU has also been shown to possess activity in ovarian carcinoma [33], investigators at the National Cancer Institute conducted a phase II trial of this agent, delivered by the intraperitoneal route, in patients with refractory ovarian carcinoma [34]. This treatment program called for 5-FU to be administered at a concentration of 4 mM in eight consecutive two-liter dialysis exchanges (four-hour duration/exchange). The procedure was repeated every two weeks for six cycles unless there was evidence of disease progression. Unfortunately, only one of 14 patients (7 percent) responded to the treatment program; this individual experienced a surgically defined complete response, and a majority of patients participating in this program had previously received systemically delivered 5-FU. As most initial intravenous treatment regimens in ovarian carcinoma do not currently include 5-FU, it is possible greater activity would now be observed for this drug delivered by the intraperitoneal route in the refractory disease setting [22].

Doxorubicin

Doxorubicin is an active drug in the treatment of ovarian carcinoma and pre-clinical data has suggested that it might be very effective in this disease when delivered by the intraperitoneal route [33,35–36]. Unfortunately, while responses to intraperitoneal doxorubicin in refractory ovarian carcinoma have been observed, local toxicity (abdominal pain, adhesion formation, ascites production) has been severe [37–39]. Abdominal pain was observed in most patients with intraperitoneal doxorubicin doses of $\geq$20 mg. In view of this toxicity pattern, investigators have not continued to pursue the use of this agent for intraperitoneal administration in ovarian carcinoma.

Mitoxantrone

Mitoxantrone is a chemotherapeutic agent with an efficacy and toxicity pattern which is quite similar to that of doxorubicin [40]. The agent has demonstrated significant activity in ovarian carcinoma when delivered intravenously [41]. Analysis of the activity of a large number of drugs against refractory ovarian carcinoma in a short-term clonogenic assay has suggested that mitoxantrone is perhaps the most active agent against ovarian carcinoma at concentrations which can be achieved in the peritoneal cavity [42].

As the drug is known to produce far less irritation to tissues than does doxorubicin, it was quite natural that investigators at a number of institutions initiated phase I trials of intraperitoneal mitoxantrone in refractory ovarian carcinoma [43–46]. These studies have confirmed the pharmacokinetic advantage of the intraperitoneal administration of mitoxantrone and the relative safety of the agent when delivered by the intraperitoneal route; however, dose-limiting toxicity of this drug continues to be

abdominal pain and adhesion formation (with mitoxantrone doses of $\geq$20 mg/m^2). Objective responses, including surgically defined complete remissions, have been noted. Of interest is the fact that activity for intraperitoneal mitoxantrone has been observed in patients who have previously received systemically delivered doxorubicin [47]. Phase II trials of single-agent intraperitoneal mitoxantrone in refractory ovarian carcinoma are currently in progress [47].

Melphalan

Several groups have examined the intraperitoneal administration of melphalan in ovarian carcinoma [48,49]. In addition to confirming a modest pharmacokinetic advantage associated with this route of drug delivery, the drug has been shown to produce limited local toxicity. Little activity has been observed in refractory ovarian carcinoma. This result is not surprising in view of the known limited clinical utility for alkylating agents in the treatment of refractory disease [22,50,51].

The use of this agent as part of initial chemotherapy for ovarian carcinoma would be of greater interest. As the dose of intraperitoneally administered drug can be escalated to the point where systemic toxicity (bone marrow suppression) is dose-limiting, the concentration of drug reaching the tumor by capillary flow (as previously discussed in this review) should not be compromised when this route of drug delivery is employed [49].

Mitomycin-C

Mitomycin-C has been included in a number of second-line systemic regimens for ovarian carcinoma [52,53]. Several investigators have examined its use for intraperitoneal administration in ovarian carcinoma and other intra-abdominal malignancies [54,55]. Dose-limiting toxicity is the development of abdominal pain and severe adhesion formation with mitomycin doses exceeding 10 mg/m^2/course [56]. A recent report from the University of Arizona Cancer Center has demonstrated clinical responses (falls in CA-125 antigen, conversion of positive peritoneal cytologies to negative) in a number of patients with refractory ovarian carcinoma treated with intraperitoneal mitomycin (10 mg/m^2 every four weeks) [54]. At the time of the report on their initial experience using this treatment regimen, eight of the 14 treated patients remained without evidence of disease with a median follow-up of ten months.

Additional Single-Agent Intraperitoneal Trials in Ovarian Carcinoma

A number of other agents have been examined for a potential role when delivered by the intraperitoneal route in ovarian carcinoma. A pharmacokinetic advantage and limited evidence of clinical activity has been observed for methotrexate [57,58], cytarabine [59], and etoposide [60,61]. In theory, drugs with limited activity in ovarian carcinoma may be of greater interest when used in a combination intraperitoneal regimen if there is experimental evidence of concentration-dependent synergy between the drugs included in the program [5].

COMBINATION INTRAPERITONEAL THERAPY IN THE MANAGEMENT OF OVARIAN CARCINOMA

Based on previously reported data suggesting the superiority of combination chemotherapy over single agents in the management of ovarian carcinoma, it was quite

natural that combination intraperitoneal regimens would be examined in this disease [62]. A number of phase I combination intraperitoneal programs in ovarian carcinoma have been reported. Most multi-agent programs have employed cisplatin as the principal cytotoxic agent. Drugs used in addition to cisplatin have included etoposide [60], melphalan [62], 5-FU [63,64], cytarabine [65], cytarabine/doxorubicin [66], and cytarabine/bleomycin [67,68]. Cytotoxic agents have been selected based both on clinical experience employing the drugs systemically in ovarian carcinoma and on theoretical considerations (i.e., experimental evidence of concentration-dependent synergy between the agents) [5].

It is important to note that the majority of combination and single-agent intraperitoneal trials in ovarian carcinoma have not required that patients undergo a laparotomy to assess response [69]. In the absence of such information it is difficult to know if patients with small-volume residual disease (that subpopulation with the greatest chance of benefiting from intraperitoneal treatment) have actually responded to therapy. A "clinical complete repsonse" has little if any meaning in this patient population, and published studies utilizing this end-point must be interpreted with caution. While overall survival is an important end-point, it is difficult to compare patient groups treated on different phase I or phase II trials. In addition, it is known that patients with small-volume residual ovarian carcinoma may survive for a number of years following the documentation of persistent disease after intravenous chemotherapy [70–72]. Therefore, a two- or three-year disease-free survival following intraperitoneal therapy may only reflect the natural history of disease rather than a major effect of treatment.

A recent report from the Memorial Sloan-Kettering Cancer Center of a phase II trial of combination intraperitoneal cisplatin and etoposide in refractory ovarian carcinoma has helped to define further a patient population most likely to benefit from this therapeutic approach [73]. The 20 evaluable patients with no tumor nodules >0.5 cm in diameter had a 55 percent surgically documented response rate (CR or PR) compared to a 17 percent response rate (all PRs) in the 24 evaluable patients with at least a single lesion >0.5 cm in diameter ($p = 0.019$).

Of note, a subset of patients treated on this phase II trial had *recurrent* ovarian carcinoma rather than refractory disease. Recurrent ovarian carcinoma, as defined by the Memorial group, is disease which has responded to initial therapy but which has recurred with a treatment-free interval of ≥ 1 year. Previous experience with ovarian carcinoma and other tumor types has suggested that second responses may occur in relapsing patients when the same or similar treatment is employed in individuals who have not received any treatment for a significant period of time (usually at least one year) [74–76]. In contrast to the experience in patients with refractory disease (no treatment-free interval), where responses were seen principally in individuals with the smallest tumor volumes, patients with recurrent disease had a high response rate independent of the bulk of tumor present at the initiation of treatment. These data support the argument that following intraperitoneal delivery of cisplatin there will be significant delivery of cisplatin to the tumor by capillary flow. It also emphasizes the difficulty encountered when attempting to define the precise role played by intraperitoneal drug delivery, as responses observed may be due to systemic drug uptake. The major difference in response rates based on the *volume of disease* in the refractory population suggests, however, that the route of drug administration is important in this clinical setting.

BIOLOGICAL AGENTS DELIVERED BY THE INTRAPERITONEAL ROUTE IN THE MANAGEMENT OF OVARIAN CARCINOMA

A number of biological agents have been delivered by the intraperitoneal route in the managment of ovarian carcinoma [77]. Justification for this approach is similar to that described for cytotoxic drugs, with the additional theoretical argument that high peritoneal cavity drug levels may result in the augmentation of local immunoregulatory mechanisms. Responses, including surgically defined complete remissions, have been observed in refractory ovarian carcinoma. Of note, as with cytotoxic chemotherapy, these major responses have been seen almost exclusively in patients with very small-volume residual disease [77,78]; however, even patients wiht bulky intra-abdominal disease and intractable ascites have been shown to experience clinically important palliation of symptoms secondary to a reduction in malignant fluid reaccumulation. Despite early promising results employing biological agents when administered by the intraperitoneal route, a precise role for this treatment strategy in the management of ovarian carcinoma remains to be defined.

CONCLUSION

Intraperitoneal therapy has evolved from a highly investigative treatment strategy into a form of treatment which can, under certain circumstances, be considered a reasonable option in the standard management of ovarian carcinoma. It remains to be determined, however, if the responses observed in the refractory disease setting can be translated into a major survival advantage for patients treated in this manner.

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