

Update on Chemotherapeutic Agents Utilized for Perioperative Intraperitoneal Chemotherapy

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ABSTRACT

A new strategy currently under evaluation in patients with peritoneal carcinomatosis from gastrointestinal and gynecologic cancers is perioperative intraperitoneal chemotherapy. Although results to date show benefit to carefully selected groups of patients, continued local-regional failure is seen in many treated patients. Continued clinical and laboratory research efforts to improve local-regional effects are desired. The chemotherapeutic agents that have been used in the past or are currently being tested were reviewed. Their pharmacologic properties and clinical features were collected from the medical literature and are reviewed in the text. An organized presentation of avail-

able data concerning the drugs available for perioperative intraperitoneal chemotherapy for peritoneal surface malignancy was made. From this review, new possibilities for improved doses, schedules, and drug combinations for perioperative intraperitoneal chemotherapy may become important in future clinical studies. Continued optimal utilization of intraperitoneal chemotherapy treatments in the operating room with hyperthermia or normothermic treatment in the early postoperative period is desirable. Innovative treatment strategies can improve the outcome of patients with peritoneal surface malignancy. *The Oncologist* 2005;10:112-122

INTRODUCTION

Recent reports from the oncology literature support a new approach to the prevention and treatment of peritoneal carcinomatosis. Rare diseases such as pseudomyxoma peritonei and peritoneal mesothelioma are currently managed by cytoreductive surgery with perioperative intraperitoneal chemotherapy with improved outcome. Although phase III data are lacking, current benefit versus prior treatment failure has brought about a change in the standard of practice [1-4]. Learning from the paradigm of these rare diseases,

selected patients with small-volume peritoneal carcinomatosis from colorectal malignancy are candidates for a comprehensive approach utilizing cytoreductive surgery and perioperative intraperitoneal chemotherapy. Numerous phase II and a single phase III study support a curative approach to carcinomatosis from colorectal cancer [1, 5-7]. In patients with gastric cancer with peritoneal seeding, gastrectomy plus perioperative intraperitoneal chemotherapy represents a palliative treatment option associated with a small likelihood of long-term survival. Eight different

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phase III studies reported a survival advantage when perioperative intraperitoneal chemotherapy is added to surgery in patients with primary gastric cancer. Stage III patients projected the greatest survival advantage [8]. Although benefits have been reported in the literature, a standardization of the optimal management plans for prevention or treatment of peritoneal surface malignancy has not been developed. Before this new treatment strategy gains wide acceptance, further clinical evaluation in phase III trials is needed. This manuscript reviews the pharmacologic information available for intraperitoneal chemotherapy agents that has been reported to date and identifies the factors that may be important in the utilization of one or more drugs for perioperative intraperitoneal treatments. Table 1 itemizes the pharmacologic data that will assist in the evaluation of and planning for future clinical studies.

RATIONALE FOR PERIOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

In the past intraperitoneal chemotherapy has been judged to create more logistical problems than survival benefit. Poor drug distribution from surgical adhesions, inadequate drug penetration into tumor nodules or tumor entrapped in scar tissue, and repeated failures with long-term peritoneal access have led to this conclusion. Now, using intraperitoneal chemotherapy as a planned part of a primary gastrointestinal cancer operation or cytoreduction for carcinomatosis, these logistical problems may no longer occur. In the perioperative setting, all adhesions are taken down and scar tissue is resected, visible cancer nodules are resected, and the tubes and drains are placed intraoperatively only for the duration of the treatments. The intraperitoneal chemotherapy is only required to eradicate microscopic residual disease for its complete success.

Table 1. Chemotherapy agents used for perioperative intraperitoneal chemotherapy*

| Drug | Type | Molecular weight | AUC ratio | Dose | Carrier solution | Incompatibility in solution | Heat synergy | Heat stability | Stability in solution at room temperature | Depth of penetration | Unusual local toxicity | Metabolism |
|--------------|-----------------------|------------------|-----------|--------------------------|--|---------------------------------------|--------------|----------------|---|----------------------|--|--|
| Doxorubicin | Antitumor Antibiotic | 579.99 | 230 | 15 mg/m ² | 1.5% dextrose dialysis solution | Heparin Fluorouracil | Yes | 42.0 | 7 days | 4–6 cell layers | Peritoneal sclerosis, abdominal pain with instillation | Hepatic metabolism with biliary excretion: 40%–50% Renal: 4%–5% |
| Melphalan | Alkylator | 305.2 | 93 | 70 mg/m ² | 0.9% sodium chloride | N/A | Marked | 42.0 | 2 hours | N/A | N/A | Primarily non-renal |
| Mitomycin C | Antitumor Antibiotic | 334.3 | 23.5 | 35 mg/m ² | 1.5% dextrose dialysis solution | Bleomycin | Yes | 42.5 | 58 ± 10 minutes in perfusate | 2,000 μ | Bowel perforation, anastomotic dehiscence | 25% first pass. Urine excretion: 10%–30% |
| Cisplatin | Alkylator | 300.1 | 7.8 | 90 mg/m ² | 0.9% sodium chloride | N/A | Yes | 41.5 | 20 hours | 1–3 mm | N/A | Nonenzymatic conversion, renal excretion |
| Gemcitabine | Pyrimidine antagonist | 299.5 | 500 | 1,000 mg/m ² | 0.9% sodium chloride | N/A | At 48 hours | 42.5 | Stable | N/A | N/A | Intracellular metabolism, renal excretion |
| Mitoxantrone | Antitumor Antibiotic | 517.41 | 115–255 | 28 mg/m ² | 0.9% sodium chloride, lactated Ringer's solution | Heparin | Yes | 43.0 | 7 days undiluted | 5–6 cellular layers | Abdominal pain, adhesion formation | Excretion: urine and feces |
| Oxaliplatin | Alkylator | 397.3 | 16 | 460 mg/m ² | 5% dextrose | Aluminum alkaline or NaCl solutions | Yes | 46.0 | 6 hours | 1–2 mm | N/A | Nonenzymatic biotransformation. Eliminated renal 54% and fecal 2% |
| Etoposide | Antitumor Antibiotic | 588.58 | 65 | 25–350 mg/m ² | 5% dextrose | Plastic devices, acrylic, antibiotics | Yes | 42.0 | 24–96 hours | N/A | N/A | Hepatic metabolism, elimination renal 44%–60%, fecal 16%, bile 6% |

Table 1. Chemotherapy agents used for perioperative intraperitoneal chemotherapy* (continued)

| Drug | Type | Molecular weight | AUC ratio | Dose | Carrier solution | Incompatibility in solution | Heat synergy | Heat stability | Stability in solution at room temperature | Depth of penetration | Unusual local toxicity | Metabolism |
|--------------------|----------------------|------------------|-----------|--|---|--|--------------|----------------|---|----------------------|--|--|
| Irinotecan | Antitumor Antibiotic | 677.19 | N/A | | | | No | 44.0 | 12 hours | N/A | N/A | Hepatic biotransformation SN-38, renal excretion 11%–20% |
| Paclitaxel | Antimitotic | 853.9 | 1,000 | 120-180 mg total dose | 1.5% dextrose dialysis solution, 6% hetastarch | Plastic containers and tubes | No | 42.5 | 27 hours | >80 cell layers | May leach carcinogen from soft plastic | Hepatic biotransformation. Excretion: renal 16% and bile 14% |
| Docetaxel | Antimitotic | 861.9 | 552 | 45 mg/m ² | 0.9% sodium chloride | Plastic containers and tubes | No | N/A | Use within 4 hours | N/A | May leach carcinogen from soft plastic | Excretion: fecal 75% and renal 6% |
| 5-Fluorouracil | Anti-metabolite | 130.08 | 250 | 650 mg/m ² × 5 days | 0.9% sodium chloride, Icodextrin, 1.5% dextrose dialysis solution | Daunorubicin, doxorubicin, idaurubicin, cisplatin, icytarabine, diazepam | Minimal | 43.0 | | 0.2 mm | Increased with prior radiation therapy | Hepatic degradation 90%, renal 7%-20% |
| Floxuridine (FUDR) | Anti-metabolite | 246.2 | 75 | 500 mg/m ² twice daily × 3 days | 0.9% sodium chloride | N/A | Minimal | 43.0 | 7 days | N/A | Chemical peritonitis | Hepatic degradation 100% |
| Carboplatin | Alkylator | 371.25 | 10 | | 0.9% sodium chloride | N/A | Yes | 41.5 | N/A | 0.5 mm | N/A | Renal clearance 67% |

*Doses are given for use as a single agent.

N/A = information not available

The pharmacokinetic advantage of the intraperitoneal route of drug administration has not been compromised when used as a planned part of a surgical procedure. The high molecular weight of chemotherapy agents and their water solubility (hydrophilic) cause a prolonged retention in the peritoneal space. Also, use of selected drugs under hyperthermic conditions can increase cytotoxicity at the peritoneal surface without an increase in systemic (bone marrow) toxicity. Hyperthermia reliably can improve drug penetration into tumor tissue. Finally, intraoperative use of chemotherapy allows manual distribution of the heated chemotherapy solution, allowing for a homogenous treatment of the entire abdominal and pelvic surface.

Currently, two perioperative time periods are utilized for surgically directed intraperitoneal chemotherapy. Drugs selected for use in the operating room have the physical properties of being heat enhanced and non-cell cycle specific. Their maximal effect on cancer cells should be produced in 60–90 minutes while the patient remains under general anesthesia. In the early postoperative period, before wound healing

causes significant abdominal and pelvic loculations, chemotherapy can be instilled into the peritoneal cavity with relatively uniform distribution. Drugs selected for early postoperative intraperitoneal chemotherapy (5–7 days) should have a high molecular weight to cause a long dwell time and are usually cell cycle specific. The intraperitoneal chemotherapy agents discussed are placed in one of these two categories although some have the physical properties to be used at either time.

INTRAPERITONEAL CHEMOTHERAPY ADMINISTRATION IN THE OPERATING ROOM UNDER HYPERTHERMIC CONDITIONS

Cyclophosphamide

Cyclophosphamide is the only chemotherapeutic agent approved by the U.S. Food and Drug Administration for intraperitoneal administration. This occurred as a result of its activity with ovarian malignancy. However, from a pharmacologic perspective, its need for activation by hepatic

microsomal enzymes makes it unfit from a theoretical perspective for intraperitoneal use. It is a drug with remarkable heat sensitization and is one of the few drugs that may be strongly recommended for intravenous delivery in the operating room when other heat synergized drugs, such as doxorubicin and cisplatin, are used with a hyperthermic delivery system within the peritoneal cavity. Because the drug is not thought to have any current application as an intraperitoneal chemotherapy agent, it is not listed in Table 1.

Doxorubicin

One of the earliest chemotherapy agents used in clinical trials via the intraperitoneal route was doxorubicin. The studies by Ozols et al. showed that the response rate of doxorubicin in patients with peritoneal carcinomatosis from ovarian primary was high [9]. However, in these initial studies, large single doses of intraperitoneal doxorubicin had multiple adverse side effects. The dose used was 30 $\mu\text{g/ml}$, which is 30 mg/l of intraperitoneal chemotherapy solution. The most noticeable side effect was severe abdominal pain with chemotherapy instillation, due to a marked peritoneal inflammation. This resulted in extensive intestinal fibrosis and obstruction, which precluded continued use of the high-dose intraperitoneal doxorubicin.

Sugarbaker and colleagues performed a dose escalation study with intraperitoneal doxorubicin using pharmacokinetic monitoring [10, 11]. It was determined that a low total dose (15 mg/m^2) results in a thin layering of fibrous tissue on peritoneal surfaces that has not been observed to interfere with subsequent gastrointestinal function. The drug was safely used as early postoperative intraperitoneal chemotherapy at 3 $\text{mg/m}^2/\text{day}$ in 1 liter of chemotherapy solution for 5 days or as heated intraoperative intraperitoneal chemotherapy at 15 mg/m^2 at 41.5°C in 3 liters of chemotherapy solution for 90 minutes. At our institution a large number of patients (approximately 200) have been treated with hyperthermic intraperitoneal doxorubicin in combination with cisplatin [12]. Currently, this heated drug combination administered in the operating room after optimal cytoreduction is the preferred methodology.

One of the important indications for intraperitoneal doxorubicin utilizes its sclerosing effect. It can be used effectively in the treatment of debilitating ascites when combined with intraperitoneal cisplatin. In conjunction with doxorubicin at 15 mg/m^2 , the standard dose of cisplatin is 50 mg/m^2 , used intraoperatively at 41.5°C in 3 liters of chemotherapy solution.

There are multiple reasons to recommend doxorubicin as an intraperitoneal chemotherapy agent. The area under the curve (AUC) ratio of intraperitoneal to intravenous concentration times in humans is 230. It is metabolized, at least

in part, as a single pass through the liver so there is a low likelihood of systemic complications. It can be mixed with a number of other chemotherapy agents (usually cisplatin) without pharmacologic incompatibility. Its penetration (augmented by heat [13]) is at least five cell layers, making it appropriate for the elimination of small-volume residual disease postoperatively [14].

Melphalan

Pioneering work by Howell et al. in San Diego, CA initiated studies with intraperitoneal melphalan [15]. Phase I/II studies in women with ovarian cancer established a maximal tolerable dose at 70 mg/m^2 . Furthermore, the remarkable thermal enhancement ratio of melphalan was demonstrated by in vivo and in vitro studies [16, 17]. It is now being explored with hyperthermia in a clinical trial in patients with small-volume residual carcinomatosis post-cytoreduction at a dose of 70 mg/m^2 (Washington Cancer Institute Protocol # X02380).

Melphalan has a number of features that are desirable for intraoperative intraperitoneal chemotherapy treatment. The remarkable responses seen with a wide variety of tumors in hyperthermic limb perfusion is the strongest clinical rationale for protocols to investigate this drug [18]. The drug has been used by Alexander et al. with very high response rates in isolated hepatic perfusion for colorectal liver metastases [19]. Current studies are under way to determine the pharmacology and clinical response of this drug given by heated intraoperative intraperitoneal chemotherapy (Fig. 1). Also, since the drug is extracted well from the tissues for pharmacologic studies, drug levels in small cancer nodules and in the normal peritoneal surface are being studied.

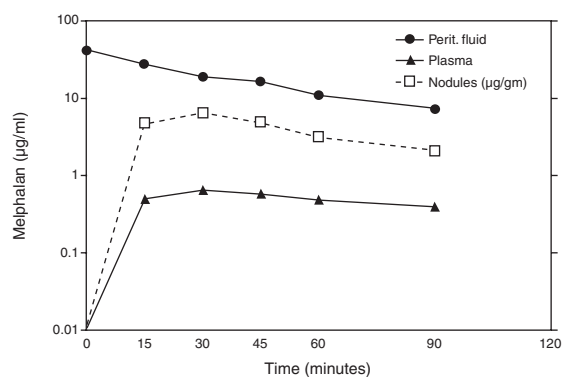


Figure 1. Heated intraoperative intraperitoneal melphalan. The drug was used at 70 mg/m^2 in 3 liters of 1.5% dextrose peritoneal dialysis solution at 42°C for 90 minutes. In this patient the AUC ratio of concentration \times time intraperitoneal to intravenous was 40. Eighty percent of the drug was cleared from the peritoneal cavity in 90 minutes. The drug concentration in the tumor nodules was approximately 30% of the intraperitoneal fluid concentration and 10 times the plasma concentration. Data were taken from study of a single patient but are very similar to data from other patients.

One caveat in dealing with this drug concerns its rapid degradation by hydrolysis. The drug should be hand delivered promptly to the operating room from the pharmacy. It should be instilled into the peritoneal cavity without delay, and the temperature of the hyperthermic solution should not exceed 42°C.

Mitomycin C

Of all the intraperitoneal chemotherapy agents used with hyperthermia, mitomycin C has been used clinically most extensively. It is usually the first agent to be selected for heated intraoperative intraperitoneal chemotherapy treatment in patients with appendiceal and colorectal carcinomas and is used in combination with other drugs in gastric malignancy.

It is recommended because of its highly favorable AUC ratio between intraperitoneal concentration times time over plasma concentration times time [20, 21]. Coadministration of chemotherapy agents is possible because of a favorable compatibility profile with many other drugs such as cisplatin and etoposide. The details of the toxicity profile, including bowel perforation and anastomotic dehiscence, have been well characterized, and surgical oncologists should be well informed of these potential adverse effects on wound healing [22, 23]. It is important to note that no cases of thrombotic thrombocytopenic purpura, also known as hemolytic uremic syndrome, have been reported with the intraperitoneal use of this drug. Hall and colleagues have recently suggested an improved management of advanced gastric cancer when intraperitoneal hyperthermic chemotherapy was added to a complete resection; the further application of hyperthermic mitomycin C to surgical treatment of gastrointestinal cancer was discussed [24]. However, there is a marked difference in drug dosimetry. When used with early postoperative intraperitoneal chemotherapy in combination with 5-fluorouracil, the suggested dose is 12.5 mg/m² for males and 10.0 mg/m² for female patients. When used as a single agent, Zoetmulder et al. determined the maximum tolerable dose can be as high as 35 mg/m² [7, 25].

Cisplatin

Cisplatin has been utilized for the past two decades through the intraperitoneal route with and without heat. The area under curve ratio of intraperitoneal concentration times time over plasma concentration times time is approximately 8, thus not as favorable as many other drugs; however, the significant cytotoxic activity against gastric cancer, ovarian cancer, and peritoneal mesothelioma have led to its frequent clinical use [26, 27].

Interesting results by Feldman et al. [4] and Sugarbaker et al. [28] showed that an ultra high dose of intraperitoneal or intrapleural cisplatin (250 mg/m²) can be administered as

an infusion when combined with thiosulfate systemically (7.5 g/m²). This combination is currently the state of art at the National Institutes of Health in Bethesda, MD for peritoneal mesothelioma after cytoreduction and at Dana Farber Cancer Institute in Boston, MA for pleural mesothelioma after pleurectomy. If the thiosulfate is given prior to or concomitant to the cisplatin, bleeding within the peritoneal cavity must not occur or cisplatin effects will be neutralized locoregionally as well as systemically.

The drug is compatible with multiple other agents, including mitomycin C, etoposide, and doxorubicin, thus constituting a logical component of the multimodality intraperitoneal chemotherapy armamentarium. Furthermore, its cytotoxicity is definitely augmented by heat. The thermal enhancement ratio that estimates the increase in cytotoxicity is 2.9 at 41.5°C [29]. The penetration of cisplatin into tumor tissue has been well documented by Los and colleagues [30, 31].

Gemcitabine

The pharmacologic studies from early 1980s suggest that cytosine arabinoside may be one of the most appropriate drugs for intraperitoneal administration. This was based on its favorable AUC ratio of intraperitoneal concentration times time to plasma concentration times time. Therefore, it is not surprising that gemcitabine, the analogue of cytosine arabinoside, has been studied for intraperitoneal administration. The pharmacology of this drug when used with moderate hyperthermia in a single patient after resection of pancreatic cancer at the Washington Cancer Institute is shown in Figure 2.

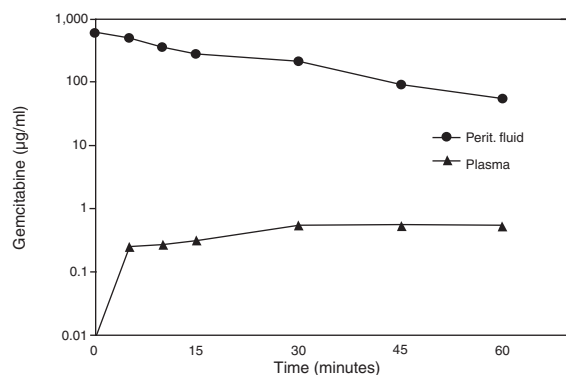


Figure 2. Heated intraoperative intraperitoneal gemcitabine. The drug was used at 1,000 mg/m² in 3 liters of 1.5% dextrose peritoneal dialysis solution at 42°C for 60 minutes. The AUC ratio of concentration × time intraperitoneal to intravenous was 500. Ninety percent of the drug was cleared from the peritoneal cavity in 90 minutes. Data were taken from study of a single patient but are similar to two others. The patient died of pancreatic cancer 29 months after combined treatment with pancreatectomy plus heated intraoperative intraperitoneal gemcitabine.

Rationale for its intraperitoneal use comes as a result of its very high AUC ratio (500 in humans and 2,225 in a rat model), when a large dose of drug (1,000 mg/m²) was used with normal renal excretion in a rat model [32]. Careful management of the drug intraoperatively with generous diuresis resulted in an absence of systemic toxicity with a profound local-regional effect. The cytotoxicity of the drug is synergized by heat if the hyperthermia is used at 48 hours after intravenous drug administration in a rat model [33]. The optimal interval between intraperitoneal drug administration and heat application has not been determined for humans.

Mitoxantrone

Link et al. from Wiesbaden, Germany, have characterized the activity of mitoxantrone for the treatment of debilitating ascites [34]. Similar to doxorubicin, this drug has a marked sclerosing effect on peritoneal surfaces. The profound cytotoxicity of this drug combined with the induction of fibrosis makes it an ideal agent for the treatment of debilitating ascites. In phase I/II studies, Link et al. determined that a single intraperitoneal instillation of 28 mg/m² is well tolerated. Over 90% of patients were palliated with a maximum of three intraperitoneal doses of drug.

An interesting observation with mitoxantrone comes about as a result of its bluish discoloration of tissues. The marked heterogeneity of intraperitoneal chemotherapy distribution after prior surgery has been well documented by the patchy blue coloration of peritoneal surfaces seen at reoperation in patients treated with intraperitoneal mitoxantrone.

The drug at doses utilized via the intraperitoneal route does not show cardiac toxicity. It should be noted that this is one of the few chemotherapy agents that has been used both in the operating room with hyperthermia and in the infusion center in a normothermic manner.

Oxaliplatin

Oxaliplatin is a new agent whose clinical use with intraperitoneal administration has been pioneered by Elias and Sideris in Villejuif, France [35]. Its administration at this institution is unusual in that a very short pulse of high-dose (460 mg/m²) oxaliplatin is used. The dwell time is only 30 minutes. The very low AUC ratio of intraperitoneal concentration times time to plasma concentration times time suggests that this drug is rapidly absorbed and does not require a long dwell time in the peritoneal cavity for maximal local-regional effect. The results of intraperitoneal treatment in patients with peritoneal carcinomatosis from colon cancer showed 67% survival at 3 years with complete cytoreduction. This group attributed their excellent results to proper patient selection, optimal cytoreduction, and heated intraoperative intraperitoneal oxaliplatin chemotherapy [36]. The

lack of neurotoxicity when given via the intraperitoneal route should be emphasized for clinical interest.

Elias and coworkers suggest that the drug should only be given if the systemic circulation has been primed with 5-fluorouracil [35]. This is the first combination of heated intraoperative intraperitoneal chemotherapy with intraoperative intravenous chemotherapy. Theoretically, the 5-fluorouracil in the systemic circulation should be targeted to the peritoneal surface by intraperitoneal hyperthermia. With heat, this drug treats the carcinomatosis nodule via the capillary network; the hyperthermic oxaliplatin treats the carcinomatosis nodule by diffusion from the intraperitoneal fluid. This bidirectional administration may result in improved response and needs to be further studied.

One caveat with oxaliplatin regards the ultra high dose advocated by Elias. The dose of 460 mg/m² far exceeds the maximum tolerable dose of drug when given systemically. If there is erratic absorption, perhaps due to total peritonectomy or if the time for peritoneal lavage is extended, excessive toxicity could occur at this high dose of drug. Therefore, more clinical trials are warranted.

Etoposide

Little experience in North America and Europe with etoposide has been published. However, in Japan, the early research with peritoneal carcinomatosis from gastric primary, utilizing combination treatment with etoposide, mitomycin C, and cisplatin, has been reported [37, 38]. Limited but definite benefits were demonstrated when palliative gastrectomy was combined with intraperitoneal heated multidrug treatment in gastric cancer patients with limited peritoneal seeding [8].

Irinotecan

Irinotecan is a new drug that is finding its way into clinical and laboratory research with peritoneal carcinomatosis [39]. Guichard et al. have shown a preference for intraperitoneal versus intravenous route of administration [40]. The high level of activity of this drug, when used in combination with 5-fluorouracil, suggests its potential role in the future treatment as an intraperitoneal drug for gastrointestinal carcinomatosis.

Some problems between the pharmacology of this drug and its application in humans deserve special mention. Irinotecan is a prodrug that has no cytotoxic effects except when it is converted to SN-38. Also, the drug metabolism and, consequently, the pharmacokinetics are much different in the laboratory animal than in humans, thus further complicating its direct clinical application.

Patients with Gilbert's syndrome should not receive irinotecan; the absence of liver enzymes that cause drug degradation in these patients causes the drug to be very toxic.

NORMOTHERMIC INTRAPERITONEAL CHEMOTHERAPY ADMINISTRATION FOR EARLY POSTOPERATIVE TREATMENT (POSTOPERATIVE DAYS 1-5)

Paclitaxel

A chemotherapy agent with wide application for gastric cancer, ovarian cancer, and mesothelioma is paclitaxel. The extremely favorable AUC ratio of intraperitoneal concentration times time to plasma concentration times time (1,000) and the remarkable drug penetration of up to 80 cell layers deserve further attention [41, 42].

Mohamed and Sugarbaker studied its use with a high molecular weight carrier solution (6% hetastarch), suggesting an increased drug exposure to peritoneal surface cancer nodules without any increase in systemic toxicity [43]. A larger total volume of chemotherapy solution retained in the peritoneal space resulted in a greater surface area exposed to the chemotherapy.

A potential problem with the use of intraperitoneal taxanes involves the lipid solvent and the fact that potential carcinogen (DEHP) can be leached out of soft plastic with paclitaxel infusions. The use of hard plastic bags and tubing can eliminate these potential adverse events.

Paclitaxel is currently used for treatment of debilitating ascites with favorable results. Its use in early postoperative intraperitoneal chemotherapy in peritoneal mesothelioma patients is associated with a marked prolongation of median survival in this selected subset of patients [3].

Docetaxel

Another taxane that has promise as a normothermic intraperitoneal lavage is docetaxel. Similar to paclitaxel, docetaxel is minimally enhanced by heat. Studies by de Bree et al. showed a very favorable AUC ratio and a high level of activity with ovarian cancer [44]. Currently, Fushida et al. in Japan are using this as part of neoadjuvant treatment in patients with gastric cancer with peritoneal carcinomatosis, and a high response rate has been observed [45]. De Bree et al. used this drug in hyperthermic perfusion, but the rationale for its use with heat has not been clearly established. In an animal model, Mohamed et al. showed only moderate increases in antitumor activity when this drug was combined with hyperthermia [46].

5-Fluorouracil

Perhaps one of the oldest and best studied intraperitoneal agents for gastrointestinal cancer is 5-fluorouracil. Its metabolism in a single pass through the liver following intraperitoneal administration allows for high doses of drug, i.e., up to approximately 150% of systemic dose intraperitoneally. Currently, the drug is frequently used as early postoperative

intraperitoneal chemotherapy at 650 mg/m² for the first 5 days after cytoreductive surgery for carcinomatosis from gastrointestinal cancer [12].

Its marked activity in the prevention of adhesions after major surgery deserves further comments [47]. There is improved survival of patients treated with intraperitoneal 5-fluorouracil after a potentially curative resection of primary colon cancer [48, 49]. A decrease in the incidence of carcinomatosis in a phase III trial in colorectal cancer patients at high risk for recurrence has been documented [50].

Floxuridine

Floxuridine is a unique chemotherapy agent because of its complete metabolism with a single pass through the liver from hepatic artery to hepatic veins or from portal vein to hepatic veins. For that reason it has been used extensively for hepatic artery infusion for patients with colorectal cancer metastases to the liver. Kelsen et al. reported a phase I/II trial of intraperitoneal floxuridine and systemic 5-fluorouracil in patients at high risk for local-regional recurrence after the resection of colon cancer [51]. No liver metastases and no peritoneal carcinomatosis occurred in this group of 26 patients. This approach was thought to deserve further trials. Crookes et al. used floxuridine as neoadjuvant treatment for poor-prognosis gastric cancer patients with promising preliminary results [52]. Newman and colleagues continue to use intraperitoneal floxuridine in gastric cancer in studies at New York University [53].

Carboplatin

Carboplatin has been used by the intraperitoneal route by the Netherlands Cancer Institute for the treatment of ovarian malignancy [54]. Studies by Los et al. suggest that carboplatin has less penetration into tissues as compared with cisplatin in a rat model [31]. Currently, it is not considered an important agent for intraperitoneal administration.

DISCUSSION

Numerous phase II studies showing a high cure rate with epithelial malignancy of the appendix with peritoneal dissemination (pseudomyxoma peritonei syndrome) and a lack of other successful treatment alternatives have led to a consensus regarding the management of this condition. A comprehensive treatment using cytoreductive surgery with peritonectomy plus perioperative intraperitoneal chemotherapy is the treatment of choice [1, 2]. Usually, this requires referral to a peritoneal surface malignancy treatment center for definitive management with cure as the goal.

Although long-term survival has been less conclusively demonstrated with peritoneal mesothelioma, the prolonged benefit recently reported with this disease suggests that the

routine application of an aggressive local-regional approach is the preferred strategy [3, 4]. Again, the lack of any other successful strategy that competes with comprehensive treatment is an important factor in a recommendation of this approach as a standard of care.

Currently, recommendations for routine application of comprehensive treatment in colorectal and gastric cancer with peritoneal seeding are less secure. Certainly, systemic chemotherapy does not provide any patient with a hope for cure. The combined approach when used in peritoneal carcinomatosis from colorectal cancer is supported by results from numerous phase II studies at different institutions [55]. The 5-year survival rate of approximately 30% is consistent in all reports. There is a single phase III prospective, randomized study that compared an aggressive combined approach with standard treatment with systemic chemotherapy [7]. The median survival with combined treatment was 22.3 months and for the control it was 12.6 months ($p = 0.032$). The morbidity and mortality associated with this treatment compares favorably with that reported for the surgical management of large surgical procedures for gastrointestinal cancer [22, 23]. It may be suggested that sufficient data have accumulated to move this strategy from clinical research to standard of practice [56]. The survival reported by numerous groups is comparable with that observed with other abdominopelvic malignancy such as retroperitoneal and visceral sarcoma, gastric cancer, and liver metastases from colorectal cancer. The survival is far superior to some cancers that are routinely resected, such as pancreatic cancer, gallbladder cancer, and cholangiocarcinoma. By analogy with other standard of practice management plans, the efficacy of these carcinomatosis treatments and the morbidity and mortality are acceptable.

Although cytoreductive surgery plus intraperitoneal chemotherapy has met with considerable success, clinical pathways that result in no local-regional recurrence after aggressive combined treatment have not occurred. A majority of patients who recur develop a regrowth of cancer on abdominal or pelvic surfaces. With further clinical research efforts, the results of intraperitoneal chemotherapy treatments will certainly improve. The treatment options for the perioperative intraperitoneal chemotherapy are large. The priorities for developing further treatment options will be difficult because of the long list of possibilities. The decisions will concern not only the chemotherapy response for the site of the primary cancer (appendix versus colorectal versus gastric versus ovary, etc.) but also the physical characteristics selected for the treatment such as hyperthermia versus normothermia, open versus closed abdomen, intraoperative intraperitoneal chemotherapy versus early postoperative intraperitoneal chemotherapy versus both intraoperative and early postoperative intraperitoneal

chemotherapy, single drug versus multiple drugs, intraperitoneal administration only versus combined intraperitoneal and systemic chemotherapy administration, high-dose (pulsed) treatments versus longer-term moderate dose treatments, isotonic versus hypertonic carrier solution, and short versus long dwelling time.

An important consideration in the design of future protocols will be selection of combination chemotherapy that shows drug synergy. Elias and Sideris have successfully used systemic intraoperative 5-fluorouracil and heated intraoperative intraperitoneal oxaliplatin in patients with colorectal carcinomatosis [35]. Feldman et al. have used systemic thiosulfate to mitigate against systemic complications of high-dose heated intraoperative intraperitoneal cisplatin [4]. For example, combinations of systemic cisplatin and intraperitoneal gemcitabine would provide a broad spectrum of antitumor effects. Also, giving one drug intravenously and a second drug intraperitoneally would avoid the chemical incompatibilities that occur. For example, chemotherapy in the taxane category that is lipid soluble cannot be used with hydrophilic drugs. Also, 5-fluorouracil, not miscible with most other chemotherapy agents, can be used intravenously with other drugs used intraperitoneally.

This manuscript and the accompanying chart are designed to assist the clinical researcher in the formulation of future studies in patients with peritoneal surface malignancy. A comparative study of the pharmacology of the chemotherapy agents currently available may be of value in making decisions regarding priorities for future investigations.

An essential part of future studies using combined treatment for carcinomatosis regards possible palliative benefits that may result. Will the patients who are not cured be palliated by a longer survival with improved quality of life? As the treatments become more thoroughly evaluated, management strategies for patients whose surgical outcome shows possible cure may have a different approach than those that can only achieve palliative debulking. If gross tumor can be resected and bowel loops separated to allow access for intraperitoneal chemotherapy, palliative treatment protocols to prolong life and maintain quality of life by slowing the progress of intestinal obstruction may be tested.

An important caveat is required as these treatments are expanded to a greater number of patients with additional indications. Only experienced teams with proven and published favorable results should participate [57]. There is a long and steep learning curve for the surgery. Proper selection of patients for this management plan is not simple; radiologic tests are only of limited value. Also, intraoperative decisions regarding a potentially curative approach with combined treatment versus palliative debulking require extensive experience. Perhaps most problematic,

surgeons with the responsibility for intraoperative intraperitoneal chemotherapy may have little knowledge regarding the use of the potentially lethal drugs they will deliver. The opportunity for severe surgical complications and adverse drug reactions are many.

Future Plans

Continued success with this new approach to the peritoneal surface component of cancer requires additional laboratory and clinical research. In the laboratory, the ideal drugs and drug combinations for specific diseases need to be determined. In the clinics, proper selection factors that will allow treatment of patients most likely to benefit and exclusion of those who may undergo unnecessarily aggressive surgical treatments are necessary. Primary colon cancer patients at high risk for the progression of peritoneal surface malignancy need to be studied within a prospective and randomized phase III effort. In patients with established carcinomatosis, a

prospective multi-institutional study with a carefully designed and uniform treatment would be appropriate. Similarly, in gastric cancer additional phase III studies in patients with gastric cancer resected for cure are necessary. A large and adequately powered study in Western gastric cancer patients is a high-priority protocol. In gastric cancer patients with established carcinomatosis, a multi-institutional phase II study with uniform treatment parameters would be appropriate. Efforts to combine systemic with local-regional chemotherapy as part of the surgical intervention are necessary. The role of this strategy in the treatment of primary ovarian cancer or in salvage surgery for patients with recurrent ovarian cancer remains to be established. Patients with primary endometrial cancer, a disease that tends to recur locally as a result of lymphatic leakage from transected tissues, is a disease requiring further clinical studies. In all these situations, the ethical problems that arise in randomized studies in a disease that was in the past uniformly fatal will repeatedly occur.

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