TOPIC HIGHLIGHT

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Pharmacologic rationale for treatments of peritoneal surface malignancy from colorectal cancer

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Abstract

The peritoneal surfaces of the abdomen and pelvis are important sites for the dissemination of gastrointestinal and gynecologic malignancy. Transcoelomic dissemination of cancer cells gives rise to carcinomatosis, which, without special treatment, is a fatal manifestation of these diseases. To treat peritoneal carcinomatosis, cytoreductive surgery removes gross disease plus perioperative intraperitoneal and perioperative intravenous chemotherapy eradicates microscopic residual disease and chemical compatibilities. Chemotherapy agents are administered either by the intraperitoneal or intravenous route, based on their pharmacologic properties. A peritoneal-plasma barrier, which retards the clearance of high molecular weight chemotherapy from the peritoneal cavity, results in a large exposure of small cancer nodules on abdominal and pelvic surfaces. Tissue penetration of the intraperitoneal chemotherapy is facilitated by moderate hyperthermia (41-42℃). Targeting of intravenous chemotherapy to the peritoneal surface is facilitated by the intraperitoneal heat. A constant dose of chemotherapy agent and volume of carrier solution, based on body surface area, allows prediction of systemic drug exposure and systemic toxicity. Timing of the hyperthermic chemotherapy as a scheduled part of the surgical procedure to uniformly expose all peritoneal surfaces is crucial to success.

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INTRODUCTION

The peritoneal surface remains a prominent failure site for patients with gastrointestinal and gynecological cancer. In addition to the lymphatic and hematogenous routes of dissemination, transcoelomic spread of malignant cells is an acknowledged phenomenon that ultimately gives rise to peritoneal carcinomatosis (PC). This intraperitoneal spread can occur before surgery as a direct consequence of full-thickness invasion of the involved organ by tumor and exfoliation of cancer cells into the peritoneal cavity. In addition, intraperitoneal spread might be the result of surgical trauma that causes release of tumor cells from

transected lymph and blood vessels and manipulation of the primary tumor. A review of 2756 patients by Jayne *et al*[1] reported the incidence of PC at the time of initial surgery to be 7.7%. Brodsky *et al*[2] suggested that in colonic cancer patients who have recurrences, peritoneal seeding occurred in 25%-35% of patients.

NATURAL HISTORY OF PERITONEAL CARCINOMATOSIS

Nevertheless, little was done to clarify the impact of peritoneal seeding upon survival until the report of Chu and colleagues was published[3]. These investigators studied 100 patients with non-gynecologic malignancy who had biopsy-proven peritoneal carcinomatosis. The mean survival of 45 colorectal cancer patients was 8.5 mo. The presence or absence of ascites was an important poor prognostic variable in these patients.

In 2000, Sadeghi and coworkers reported on 370 patients with peritoneal carcinomatosis from non-gynecologic malignancies who were enrolled in a European prospective multicenter trail [Evolution of Peritoneal Carcinomatosis 1 (EVOCAPE 1)][4]. These patients had the benefit of fluorouracil (5-FU)-based systemic chemotherapy, but the results were remarkably similar to those reported by Chu[3] a decade earlier. The mean survival of 118 patients with carcinomatosis from colorectal cancer was 6.0 mo.

In 2002, Jayne and colleagues from Singapore used a database of 3019 colorectal cancer patients to identify 349 (13%) with peritoneal carcinomatosis[1]. Of special interest were the 125 patients (58%) who had synchronous primary colorectal cancer and peritoneal implants. The median survival of those patients was only 7 mo. The authors reported that survival was adversely affected by the extent of the peritoneal carcinomatosis and the stage of the primary cancer.

REVISED HYPOTHESIS REGARDING CARCINOMATOSIS AS LOCAL-REGIONAL CANCER DISSEMINATION

More recent chemotherapy, based on the use of oxaliplatin, irinotecan, and biological agents, has improved survival in patients with metastatic colon cancer to 16-20 mo[5-7]. Unfortunately, none of the trials using modern systemic chemotherapy provide data of results in patients with isolated PC, and only address results in a collection of patients with metastatic colonic cancer at many different anatomical sites. In the past, oncologists have assumed that PC is equal to distant metastases and as such regarded it as beyond current treatment modalities. Over the last two decades a group of oncologists have worked using a revised hypothesis. Novel therapeutic approaches have emerged for patients with isolated peritoneal metastases of gastrointestinal cancer, ovarian cancer, and primary peritoneal malignancies. Early investigators considered PC as a local-regional disease warranting a local-

regional chemotherapy (intraperitoneal) treatment. Spratt *et al*[8] reported for the first time in 1980 the use of heated triethylenethiophophoramide (thiotepa) in a patient with pseudomyxoma peritonei[8]. Koga *et al*[9] reported the use of intraperitoneal chemotherapy in 23 gastric cancer patients with PC. Speyer in 1980 used normothermic intraperitoneal 5-fluorouracil and methotrexate in 16 patients with PC[10].

ROLE FOR CYTOREDUCTIVE SURGERY

A second essential component of the modern management of PC is cytoreductive surgery with peritonectomy procedures. The rationale for a combined approach is as follows: an aggressive surgical approach combining visceral resections and peritonectomy procedures should address the macroscopic peritoneal surface disease; the perioperative intraperitoneal chemotherapy treats any residual microscopic disease[11]. The perioperative intraperitoneal chemotherapy includes hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC). More recent protocols advocate bidirectional (simultaneous intraperitoneal and intravenous chemotherapy) intraoperative chemohyperthermia. This two-component approach to PC treatment requires that chemotherapy be used as a planned part of the surgical procedure. Critical to the success is proper timing of the chemotherapy in its relation to the surgery. This innovation of combined treatment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy might be the paradigm shift responsible for recent successes *vs* prior failures in treating PC patients.

RESULTS IN TREATING CARCINOMATOSIS FROM COLORECTAL CANCER

Several phase II studies have explored the intraperitoneal route of drug delivery and show promising results in a variety of PC patients. In colorectal cancer with PC, overall survival rates between 25% and 47% are reported[12-17]. These reports, from many different institutions, stand in strong contrast with historical control groups and patients treated with systemic chemotherapy, where the mean and median overall survival were 6.0 and 3.1 mo, respectively[4]. Verwaal *et al*[18] in a phase III trial randomized treated patients with colorectal PC by palliative surgery followed by fluorouracil-leucovorin systemic chemotherapy *vs* maximal cytoreduction plus HIPEC with mitomycin C and subsequent systemic chemotherapy. This report showed a significant survival benefit for the HIPEC arm, with a median survival of 22.3 mo *vs* 12.6 mo in the control group. Glehen *et al*[19] collected data retrospectively on 506 PC patients from 28 institutions treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy. He reported an overall median survival of 19.2 mo. Patients in whom cytoreduction was complete had a median survival of

32.4 mo *vs* 8.4 mo in the patients with incomplete cytoreduction.

The clinical evidence in the medical literature supporting the combined approach of cytoreductive surgery and perioperative intraperitoneal chemotherapy is growing[20-24]. What is lacking is clear understanding of the pharmacology of the perioperative use of chemotherapy in the treatment of peritoneal surface malignancy. It is possible that increased safety and important treatment innovations might originate from analyzing the pharmacologic data. This review aims to clarify the pharmacokinetic and pharmacodynamic data currently available regarding the intraperitoneal delivery of cancer chemotherapy agents in patients with PC.

THE PERITONEAL PLASMA BARRIER

The rationale for administering chemotherapeutic drugs directly into the peritoneal cavity is supported by the relative transport barrier that is formed by the tissue surrounding the peritoneal space. The peritoneum is a complex three-dimensional organ covering the abdomino-pelvic organs and the abdominal wall. It contains a large potential space. The most elaborate description of the ultra structure of the peritoneum in man goes back to 1941 by Baron *et al*[25]. The peritoneum consists of a monolayer of mesothelial cells supported by a basement membrane and five layers of connective tissue, which account for a total thickness of 90 μm. The connective tissue layers include interstitial cells and a matrix of collagen, hyaluron, and proteoglycans. The cellular component consists of pericytes, parenchymal cells, and blood capillaries. The complex is often referred to as the peritoneal membrane. This description is a working model derived from research regarding the peritoneum as a dialysis membrane.

The accepted function of the peritoneum is twofold. First, it reduces friction between intraabdominal organs and the abdominal wall by producing a lubricant solution made of glycosaminoglycans and phospholipids[26]. Secondly, it is of major importance, together with lymphoid aggregates dispersed on the visceral and parietal peritoneum, in the host defense against intraabdominal infections. A third suggested function of the peritoneum in malignancy might be its role as a first line of defense against peritoneal carcinomatosis[27]. Any disruption in the peritoneal lining facilitates a transition from adhesion to invasion of cancer cells, resulting in the development of peritoneal tumor nodules on the abdominal or pelvic surface[27,28].

Contrary to intuitive thinking, the elimination of the mesothelial lining, as performed during peritonectomy procedures, does not significantly alter the pharmacokinetic properties of the peritoneum in the transport of chemotherapeutic agents from the peritoneal cavity to the plasma compartment. Flessner *et al*[29] demonstrated in a rodent model that neither removal of the stagnant fluid layer on the mesothelium nor removal of the mesothelial lining influenced the mass transfer

coefficient over the barrier. Evidence supporting this hypothesis in humans is supported by the fact that the extent of the peritonectomy in PC patients does little to alter the intraperitoneal chemotherapy pharmacokinetics of mitomycin C or 5-fluorouracil[30,31]. The current thinking regards not only the mesothelial lining, but also the blood capillary wall and the surrounding interstitial matrix as the principal barrier for clearance of molecules from the abdominopelvic space[32].

Much of the laboratory research concerning the pharmacokinetic properties of the peritoneum is derived from the peritoneal dialysis literature[33]. A simplified mathematical diffusion model considers the plasma to be a single compartment separated by an effective membrane from another single compartment, the peritoneal cavity. Although this offers a conceptual model of transport and states the importance of the effective exposure area, it only offers quantitative predictability once permeability is empirically determined for each drug. It also does not offer insight into the actual tissue penetration at the level of the peritoneal membrane. Neither does it predict penetration of chemotherapy into the tumor nodules, which is the single most important factor determining response to cancer treatment.

PHARMACOKINETIC RATIONALE OF PERIOPERATIVE INTRAPERITONEAL CANCER CHEMOTHERAPY

Intraperitoneal administration of chemotherapeutic agents gives high response rates in PC patients because retention of chemotherapy in the peritoneal plasma barrier provides dose-intensive therapy. Dedrick *et al*[34] in 1978 concluded that the peritoneal permeability of a number of hydrophilic anticancer drugs might be considerably slower than the plasma clearance of that same drug. This results in a significantly greater concentration in the peritoneal cavity, as compared to the plasma, after intraperitoneal administration. This concentration difference causes increased exposure of small residual tumor cells after cytoreduction to high doses of chemotherapeutic agents, with reduced systemic concentrations and lower systemic toxicity. This advantage is expressed by the Area Under the Curve (AUC) ratios of intraperitoneal *vs* plasma exposure. Table 1 presents molecular weight and AUC ip/iv for drugs in clinical or experimental use in PC patients[35].

An important consideration is that high intraperitoneal concentration or AUC ip/iv does not automatically confer a greater efficacy. Even with greatly elevated intraperitoneal cancer chemotherapy concentrations, there may be limited penetration of the chemotherapeutic agent into the peritoneal tumor target. The ideal drug for intraperitoneal chemotherapy has not only a high peritoneal tissue concentration as a result of direct intraperitoneal administration, but also a high penetration into the cancer nodule. Retention of cancer chemotherapy in preperitoneal tissue and cancer nodules is augmented by slow diffusion through the capillary endothelium, deep

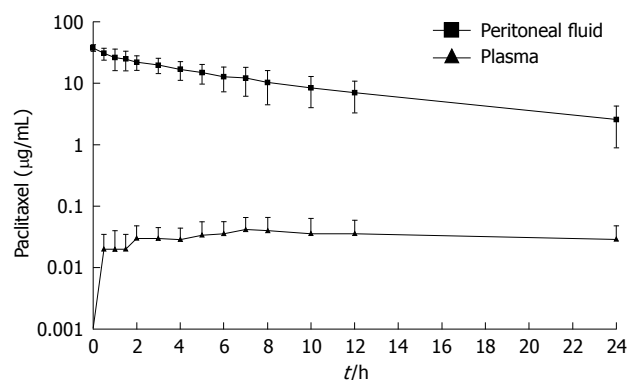| Table 1 Molecular weight and area under the curve ratios of intraperitoneal exposure to systemic exposure of chemotherapeutic agents used to treat peritoneal carcinomatosis		
Drug	**Molecular weight (Daltons)**	**Area under the curve ratio**
5-fluorouracil	130.08	250
Carboplatin	371.25	10
Cisplatin	300.1	7.8
Docetaxel	861.9	552
Doxorubicin	579.99	230
Etoposide	588.58	65
Floxuridine	246.2	75
Gemcitabine	299.5	500
Irinotecan	677.19	N/A
Melphalan	305.2	93
Mitomycin C	334.3	23.5
Mitoxantrone	517.41	115-255
Oxaliplatin	397.3	16
Paclitaxel	853.9	1000
Pemetrexed	597.49	40.8

N/A: Not available.

in the subperitoneal space of the cancer chemotherapy solution. Low systemic concentrations and reduced systemic toxicity are maintained by rapid metabolism and excretion of drug within the body compartment.
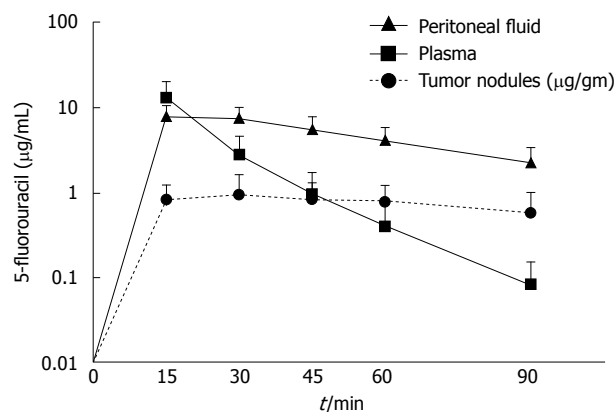
The marked increase in exposure of peritoneal surfaces to chemotherapy solution, as compared to plasma, is illustrated in Figure 1. The chemotherapy agent, paclitaxel, has a high molecular weight (853.9 Daltons) and is slow to cross the peritoneal cavity to plasma barrier. The naked molecule of paclitaxel is highly lipophilic. It is unique in cancer chemotherapy in that the intravascular or intraperitoneal administration of the drug requires it to be suspended in a detergent that maintains the drug in solution. The detergent molecules surround the paclitaxel molecule giving it additional size and a hydrophilic character. This large molecular size and hydrophilic behavior of the complex molecule result in slow passage across the peritoneal to plasma barrier. The AUC ratio for paclitaxel is approximately 1000 (Table 1).

PHARMACOKINETIC RATIONALE OF PERIOPERATIVE INTRAVENOUS COLORECTAL CANCER CHEMOTHERAPY

New pharmacological data suggests altered pharmacodynamics of intravenously administered cancer chemotherapy drugs when used intraoperatively during a HIPEC procedure. Figure 2 shows 5-fluorouracil concentrations in the plasma, peritoneal fluid, and tumor nodules after intravenous administration at the beginning of the HIPEC procedure. Almost immediately after intravenous administration, the 5-fluorouracil is transported from the plasma compartment to the expanded peritoneal cavity. There it is retained in the artificial ascites created by the HIPEC for a substantial amount of time, before reabsorption into the systemic compartment occurs. The metabolism of 5-fluorouracil

Figure 1 Pharmacokinetic study of concentration *vs* time for intraperitoneal paclitaxel. The chemotherapy agent at 30 mg/m^2 was instilled directly into the peritoneal cavity as rapidly as possible in a 1.5% dextrose peritoneal dialysis solution. The concentration of paclitaxel was determined in peritoneal fluid and in plasma for 24 h.
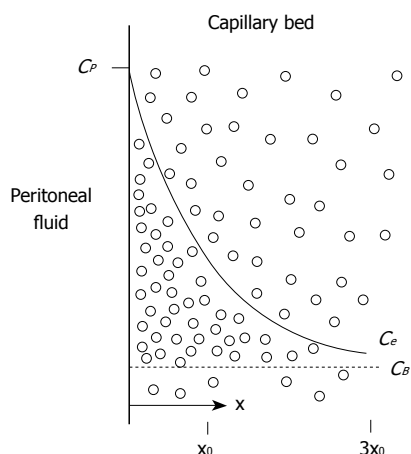

Figure 2 Pharmacodynamics during HIPEC after intravenous administration of 400 mg/m^2 of 5-fluorouracil given simultaneously with intraperitoneal chemotherapy in 3 L of chemotherapy solution. (Van der Speeten K, Stuart OA, Sugarbaker PH. Pharmacology of perioperative 5-fluorouracil. Submitted for publication).

in the ascites fluid is greatly reduced as compared to metabolism in the plasma. Our data suggests that the artificial ascites created by the HIPEC provides a reservoir for the intravenously administered drug. The intraoperative administration of intravenous cancer chemotherapy might offer a pharmacologic advantage in killing residual tumor cells after cytoreduction. Timing of intravenous cancer chemotherapy (intraoperative *vs* pre- or postoperative) emerges as a new variable, which could affect efficacy of cancer chemotherapy drugs in treating patients with a peritoneal surface malignancy.

Tissue distribution and penetration depth
The simplified two-compartment model described by Dedrick and colleagues might not provide an adequate theoretical model for penetration of the intraoperatively administered (either intravenous or intraperitoneal) chemotherapy into the preperitoneal tissues and into the tumor nodules. Dedrick *et al*[36,37] proposed a mathematical model (Figure 3) addressing the tissue penetration of low-molecular weight molecules. The drug diffuses from its peritoneal
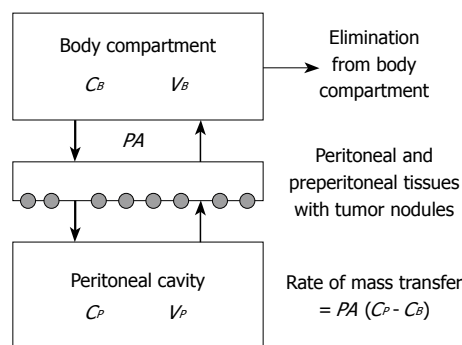
Figure 3 Conceptual diagram of tissue adjacent to the peritoneal cavity. C_P = the free drug concentration in the peritoneal fluid; C_B = the free drug concentration in the blood (or plasma). Solid line shows the exponential decrease in the free tissue interstitial concentration, C_e, as the drug diffuses down the concentration gradient and is removed by loss to the blood perfusing the tissue. Also shown are the characteristic diffusion length, x_0, at which the concentration difference between the tissue and the blood has decreased to 37% of its maximum value, and $3x_0$, at which the difference has decreased to 5% of its maximum value[36].

Figure 4 Three-compartment model of peritoneal transport, in which transfer of a drug from the peritoneal cavity to the blood occurs across the peritoneal membrane and preperitoneal tissues. The peritoneal surface cancer nodules are located in these tissues. The permeability-area product (*PA*) governs this transfer and can be calculated by measuring the rate of drug disappearance from the cavity and dividing by the overall concentration difference between the peritoneal cavity and the blood (B). C_B = the free drug concentration in the blood (or plasma); V_B = volume of distribution of the drug in the body; C_P = the free drug concentration in the peritoneal fluid; V_P = volume of the peritoneal cavity[36].

concentration, C_p, to its blood concentration, C_B, along an exponential concentration gradient over the peritoneum and preperitoneal tissues. The extracellular "deep" concentration, C_e, can then be calculated according to the formula: $C_e = C_B + (C_p - C_B) \exp[-(k/D)^{1/2}x]$. In this formula, k (min^{-1}) is the rate constant for removal of the active drug from the tissue. Movement through the tissue is characterized by the diffusivity, D (cm^2/min) and x is the distance from the serosal surface (cm). This model implies that there is an exponential concentration decrease of the drug from abdominopelvic cavity across the membrane to the plasma compartment. Consequently, the depth of penetration of the intraperitoneal concentration is very limited and is in the order of 1 to 2 mm[38,39]. Ozols *et al*[40] confirmed adriamycin penetrating only four to six cell layers of a tumor on the diaphragm in a rodent model. In all likelihood, there is variable penetration for each drug and type of tumor.

This has important consequences for implementing perioperative chemotherapy in PC patients. The cytoreduction needs to resect all tumor deposits greater than 1-2 mm for the subsequent intraperitoneal chemotherapy to be effective. Clinical data to support this pharmacologic prediction is strong; in univariate and multivariate analysis, complete cytoreduction (cancer nodules ≤ 2.5 mm) is the single most important prognostic factor[15-19]. To describe the pharmacology of both intravenous and intraperitoneal chemotherapy used after cytoreduction to treat PC, a revised theoretical model is needed. Figure 4 shows a three-compartment model constructed of a body compartment, intermediate compartment (peritoneal and preperitoneal tissues with tumor nodules) and peritoneal fluid. The movement of chemotherapy molecules from blood to peritoneal fluid through the intermediate compartment is rapid because of the extensive arterial and portal venous blood delivery to the intermediate tissues. The movement of chemotherapy molecules from peritoneal fluid back to portal blood would be less rapid.

There are a large number of variations in intraperitoneal chemotherapy treatment protocols. All these variations reflect attempts to improve diffusivity D, decrease the rate constant k, permeability P, or effective membrane area A. A non-exhaustive list of factors influencing these values, and thus the response of the peritoneal metastases to perioperative chemotherapy, is listed in Table 2. Some of these will be explored in greater detail.

TEMPERATURE

Adding hyperthermia to intraperitoneal chemotherapy might increase the tumor response to cancer chemotherapy drugs by several mechanisms. First, heat alone has a direct anti-tumor effect. Hyperthermia above 41℃ induces selective cytotoxicity of malignant cells. Several mechanisms for this effect have been proposed: impaired DNA repair, protein denaturation, and inhibition of oxidative metabolism in the microenvironment of malignant cells, leading to increased acidity, lysosomal activation, and increased cell death[41,42]. Cells are known to react to protein denaturation by up-regulation of heat shock proteins. This induces the development of thermal tolerance in tumor cells[43]. Thermal tolerance might cause the clinical importance of hyperthermia to be limited. Second, the cytotoxic effects of some chemotherapeutic agents are augmented by applying mild hyperthermia. Such augmented effects were postulated for doxorubicin[44], platinum complexes[45,46], mitomycin C[46], melphalan[47], docetaxel, irinotecan, and gemcitabine[48]. Third, this increased response might be the consequence of an increased penetration depth of the chemotherapeutic agent[49,50].

Jacquet *et al*[50] studied the changes in the penetration of intraperitoneal chemotherapy that are induced by moderate hyperthermia. The heat utilized within the peritoneal cavity

Table 2 Variables influencing the response of peritoneal carcinomatosis to perioperative chemotherapy

Temperature	Increase in temperature above 37℃ augments the cytotoxicity of cancer chemotherapy
Dose of intraperitoneal chemotherapy	As the dose increases the penetration of chemotherapy into cancerous tissue increases because of an increasing diffusion gradient
Distribution of chemotherapy solution and heat (open *vs* closed technique)	The open technique allows more uniform distribution of heat and chemotherapy solution because of the manual mixing of the abdominal and pelvic contents with the warm fluid
Timing of chemotherapy in relation to the timing of the surgical intervention	Using the chemotherapy with surgery allows complete distribution immediately after the total lysis of abdominal adhesions. This allows complete treatment of all peritoneal surfaces
Type of carrier solution	High molecular weight carrier solutions remain within the peritoneal cavity for a longer time period. The artificial ascites maintains the cancer chemotherapy in a large volume of fluid for an extended time period
Pressure	Pressure will increase the penetration of fluid and chemotherapy solution into normal and cancerous tissue
Volume of carrier solution	Increasing the volume of carrier solution without increasing the amount of chemotherapy will decrease the effectiveness of the treatment by lowering the diffusion gradient between the peritoneal space and the surrounding normal and cancerous tissue
Duration of instillation	Increasing the time period over which cancer chemotherapy is present within the peritoneal cavity will increase the cytotoxic effect
Vasoactive agents	Vasoactive agents will cause constriction of normal capillaries, but will not cause constriction of vessels within cancerous tissue. This will cause the chemotherapy to remain longer in the peritoneal space
Macromolecular vehicles	Coating of cancer chemotherapy by macromolecules may preferentially direct their entrance into cancerous tissue as compared to normal tissue
Drug sensitivity of the tumor	Increased responses are expected if the cancer is sensitive to the chemotherapy
Size of residual tumor nodules	The penetration of cancer chemotherapy is limited to approximately 1 mm. Therefore, large nodules greater than 1 or 2 mm in diameter will not be penetrated by intraperitoneal chemotherapy and should not be expected to be eliminated

was 41.5℃ to 42℃ in this rat model. Large and statistically significant increases in the amount of doxorubicin within tissues were demonstrated. The tissues in direct contact with the intraperitoneal chemotherapy were most affected. The concentration of doxorubicin in small bowel was doubled using intraperitoneal doxorubicin plus heat; a similar finding occurred for omental tissue and bladder tissue. Tissues at a distance such as heart muscle, did not show an increased concentration with heat.

PRESSURE
Dedrick *et al*[36] postulated that the penetration distance is equal to the square root of the ratio of the tissue diffusivity and the rate constant for drug removal from the tissue $(D/k)^{1/2}$. Unpublished observations by Flessner in a rat model showed a doubling of the extracellular space in the anterior abdominal wall of rats when the pressure of intra-abdominal peritoneal dialysis solution was raised from 0 to 4 cmH2O[29]. An increased effective diffusivity was postulated.

Animal experiments[51,52] confirmed the increased intratumoral accumulation and antitumor effect of intraperitoneal doxorubicin and cisplatin when the intra-abdominal pressure was raised. Increased intraabdominal pressure is thought to generate a convective flux that forces the drug from the peritoneal cavity into the sub-peritoneal tissue. At the same time, intraabdominal pressure might counteract the hydraulic capillary pressure and slow the outflow of the drug to the body compartment. Measurement of local cisplatin concentrations along the radii of peritoneal tumor nodules showed platinum penetration far beyond the 1 mm limit advocated by Los *et al*[39]. The clinical limit of usable intraabdominal pressure enhancement is dictated by respiratory and hemodynamic

tolerance. Clinical applications of HIPEC in intraabdominal pressure settings so far has been limited to palliating debilitating malignant ascites with laparoscopic HIPEC at 10-15 mmHg[53,54].

CARRIER SOLUTION
A variety of carrier solutions have been applied in different treatment protocols. Hypotonic, isotonic, and hypertonic solutions were explored with both low and high molecular weight chemotherapy molecules. The ideal carrier solution should enhance the exposure of the peritoneal surface and residual tumor cells to the chemotherapeutic agent. This is especially important in the setting of EPIC where maintenance of a high dwell volume of perfusate over a prolonged time period improves the distribution of the drug and the effectiveness of the treatment. Chemotherapy solutions of isotonic and hypertonic salt, dextrose, hetastarch, or icodextrin solutions have been explored. In an EPIC setting a high molecular weight solution that maintains artificial ascites showed higher drug availability because the total drug exposure depends not only on the active drug, but also on the carrier solution that maintains the peritoneal fluid volume[55-57].

In a HIPEC setting with a relatively short dwell time, one could theoretically expect a pharmacodynamic advantage of a hypotonic carrier through the mechanism of increased tissue and tumor absorption. Contrary to experimental studies supporting this hypothesis, Elias *et al*[58] showed no increase in tumor penetration in humans. A concomitant high incidence (50%) of postoperative peritoneal bleeding and severe thrombocytopenia has contraindicated the further clinical use of hypotonic carriers.

VOLUME OF CHEMOTHERAPY SOLUTION

Peritoneal metastases and free-floating tumor cells can be present anywhere on the peritoneal surface; therefore the entire surface of the abdominal and pelvic cavity is the target. Substantial differences in body composition of patients and differences in the actual HIPEC technique (open *vs* closed abdomen) will result in a wide variety of perfusate volumes. In current practice, the volume of the perfusate is chosen quite arbitrarily. Following the above stated equitation concerning mass transfer over the peritoneal-plasma membrane, increasing the solution contact area A improves the mass transfer. Keshaviah demonstrated a linear rise in mass transfer in 10 patients who were dialyzed with different volumes ranging from 0.5 up to 3 L[59]. Elias first published the importance of volume of chemotherapy in determining systemic exposure to the drug[60]. Sugarbaker *et al*[61] carried out a clinical investigation where 2 L *vs* 4 L *vs* 6 L of chemotherapy solution were administered. The dose of chemotherapy solution in these studies was constant. They showed that a more dilute intraperitoneal chemotherapy concentration retarded the clearance of chemotherapy and lead to a lesser systemic toxicity. In addition, it must be assumed that the less concentrated chemotherapy would, by the diffusion model, penetrate less into the cancer nodules and into normal tissues. These authors determined it necessary to regulate not only the chemotherapy dose but also the volume of chemotherapy solution by the patient's body surface area.

A consistent drug dose and chemotherapy solution volume might be the optimal method to predict a maximal treatment in the abdomen with predictable bone marrow toxicity. Sugarbaker and colleagues suggested that variable volume is a dangerous practice with unpredictable systemic toxicities[61]. If a chemotherapy solution is administered until the abdomen is full, the contact area will be variable because there is a great difference in the size of the peritoneal space for different patients. If the contact area is variable the total absorption of the drug cannot be predicted.

VASOACTIVE AGENTS

The literature concerning the effects of vasoactive substances in regulating peritoneal blood flow and tumor blood flow is extensive. These agents might contribute to a delayed clearance from the peritoneal cavity, because the blood flow in the peritoneal and subperitoneal vascular network will control, to a large extent, the movement of molecules across the peritoneal and subperitoneal tissues. General statements regarding the effects of vasoactive agents are confusing and sometimes contradictory, due to the variety of experimental systems, complex interactions of local-regional and systemic effects of vasopressive agents, and large differences between the neovasculature of tumor nodules and normal capillaries. Both intravenous and intraperitoneal administration of vasoactive molecules in combination with chemotherapeutic drugs has been

explored[36,62,63]. A preclinical study of the use of an intraperitoneal epinephrine plus intraperitoneal cisplatin in a rat model with PC, showed a direct correlation between the intraperitoneal epinephrine concentration and cisplatin accumulation in rat peritoneal tumor nodules[64]. Recently, Molucon-Chabrot *et al*[65] demonstrated for the first time the safe use of intraperitoneal epinephrine with intraperitoneal cisplatin in 18 patients with advanced peritoneal carcinomatosis. Tumor responses were obtained in some patients that were resistant to intravenous platinum compounds. Lindnér *et al*[66] reported that concurrent intravenous administration of vasopressin can increase the pharmacokinetic advantage of intraperitoneal administered carboplatin and etoposide, but not 5-FU. Further studies on the use of vasoactive agents to improve cancer chemotherapy responses in PC are required.
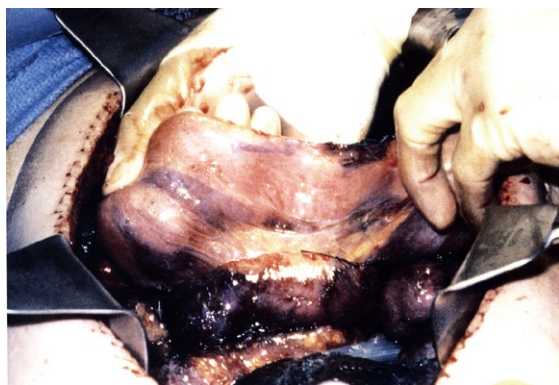
DOSE OF INTRAPERITONEAL CANCER CHEMOTHERAPY

Many different chemotherapy agents, drug concentrations, drug doses, and drugs schedules have evolved at many institutions for perioperative cancer chemotherapy. Most authors use a drug dose based on calculated body surface area (mg/m^2), although Rubin *et al*[67] demonstrated that there is an imperfect correlation between actual peritoneal surface area and calculated body surface area. The same study suggests sex differences in peritoneal surface areas that in turn might affect the absorption characteristics. Females have a larger peritoneal surface in proportion to body size than males by approximately 10%. Estimates of the functional peritoneal surface area by applying stereological methods to CT scans have been attempted[68].

Body surface area is an accurate predictor of drug metabolism and in this regard is useful for estimating systemic drug toxicity. As discussed by Sugarbaker *et al*[61], the accuracy of this prediction is increased if the volume of chemotherapy solution is also determined by the body surface area. With a constant total dose of chemotherapy and chemotherapy solution, the bone marrow exposure to cytotoxic drugs can be most accurately predicted. If these predictions are not available, the danger of overdosing some patients and underdosing others will occur.

A significant number of institutions use a closed method for intraoperative hyperthermic chemotherapy administration. In this technique, the dose of cancer chemotherapy is calculated per liter by body surface area. The total amount of cancer chemotherapy is mixed in a large volume of carrier solution (usually 6 L) that is placed in a reservoir. For example, Deraco *et al*[69,70] have used doxorubicin at 15.25 mg/m^2 per liter and cisplatin at 43 mg/m^2 per liter with the total volume of 6 L. Gilly and coworkers have used mitomycin C at 0.5 mg/kg and cisplatin at 0.7 mg/kg in a total volume of 4 to 6 L[71,72]. In this method, the amount of chemotherapy solution in contact with the peritoneal surface is determined by multiple variables, in addition to the body surface area; the amount of distention (between 2 and 6 L) of the

Figure 5 Spatial distribution of intraperitoneal methylene blue, using the closed abdomen technique. Although the subcutaneous tissues were uniformly stained, the small bowel loops showed variable staining caused by adherence of adjacent bowel loops.

abdominal cavity induced by the chemotherapy solution, the patient's sex, the amount of ascites present preoperatively and the extent of the visceral resection. This means that the peritoneal surface in contact with the chemotherapy solution is variable; consequently, the systemic absorption and the plasma concentration of the chemotherapy are variable. In this situation the systemic toxicity is not predictable.

In summary, a system that allows a variable amount of chemotherapy solution to contact peritoneal surfaces might result in a less accurate prediction of plasma AUC, because the total volume of intraperitoneal chemotherapy can vary widely betweens individuals. Increases in the volume of intraperitoneal chemotherapy solution cause an increase in diffusion surface and an increase in the amount of drug moving from peritoneal space to plasma.

Distribution of intraperitoneal chemotherapy
Both open and closed intraperitoneal chemotherapy methods of administration have been described[73-77]. The closed abdomen techniques have the theoretical advantage of less heat loss during perfusion. Also, a reduction in environmental risk for the operative team has been suggested. However, to date no study has been able to detect any occupational risk for the staff[78-80]. Open abdomen techniques will provide a better spatial distribution of the chemotherapy solution over the entire peritoneal surface. In addition, a more uniform heat distribution is expected if the chemotherapy solution is manually stirred throughout the HIPEC. Elias *et al*[76] performed a prospective phase I‑II study comparing seven HIPEC perfusion techniques. Judgments regarding adequate spatial distribution were made by measurement of temperature at multiple sites. Using the closed system, temperature varied greatly throughout the abdomen and pelvis. The temperature became more uniform with an open abdomen and manual distribution. Spatial diffusion, studied by adding methylene blue to the perfusate, was incomplete in the closed abdomen techniques (Figure 5). However, these differences in the delivery of HIPEC might be more theoretical than real. In studies to date,

only the extent of PC, the absence of extraperitoneal disease, and the completeness of cytoreduction correlated with survival. Comparison of data from centers performing either closed or open abdomen techniques, suggest that the chemotherapy effects by open or closed methods might be similar. Long follow-up will be required to make an accurate comparison.

TIMING OF CANCER CHEMOTHERAPY IN RELATION TO TIMING OF THE SURGICAL INTERVENTION

Neoadjuvant bidirectional chemotherapy
Considering the clinical application of chemotherapy in PC patients, one can intervene at four possible points in the timeline. First, neoadjuvant bidirectional chemotherapy uses both the intraperitoneal and intravenous routes of chemotherapy administration. It has been explored as an option to reduce the extent of small PC nodules. Theoretically, it might facilitate definitive cytoreductive surgery after initial exploratory laparoscopy shows PC. Radiological and clinical responses have been reported by several groups[81-83].

Although this strategy might reduce the tumor load to be addressed by cytoreductive surgery, it has several disadvantages. Adhesions from prior surgical interventions might interfere with adequate intraperitoneal drug distribution. Complete responses are very unusual, so that further cytoreduction-chemotherapy is necessary if the approach is curative. Neoadjuvant intraperitoneal chemotherapy has been reported to add to morbidity and mortality of further surgical treatment[84]. Extensive fibrosis as a response to chemotherapy might occur and make judgments concerning the extent of peritoneal carcinomatosis difficult, or even impossible, to assess.

Intraoperative intraperitoneal chemotherapy
Intraoperative intraperitoneal chemotherapy has been the most widely explored modality with consistent clinical improved outcomes in many phase II trials and several phase III trials[22-24].

Early postoperative intraperitoneal chemotherapy
Early postoperative intraperitoneal chemotherapy has some conceptual advantages. It is administered after cytoreductive surgery at the time of minimal residual tumor burden. Additionally, intraperitoneal treatments initiated before wound healing occurs can minimize non-uniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits. Proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell-cycle specific drugs such as 5-fluorouracil and the taxanes. Most EPIC regimens are administered postoperatively day 1 to 5 or day 1 to 4 through an inflow catheter and outflow drains placed at the time of cytoreductive surgery. EPIC can be applied with or without HIPEC[85].

Long-term combined intraperitoneal and systemic chemotherapy

Markman *et al*[86], Alberts *et al*[87], and Armstrong *et al*[88] demonstrated in a phase III trials that intravenous plus intraperitoneal chemotherapy improves survival in patients with optimally debulked stage III ovarian cancer, as compared to intravenous chemotherapy alone. This approach might be used as "chemotherapeutic bridging" between incomplete initial surgery and definitive cytoreduction or second look surgery. This type of chemotherapy is an adjuvant and not a perioperative use of chemotherapy. Failure analysis reported for cytoreductive surgery plus perioperative chemotherapy determined recurrent cancer most frequently occurs within the abdominal and pelvic cavity[89,90]. To optimize the treatment of patients with PC, it is likely that the greatest benefit will occur from a combination of these four treatment strategies.

DURATION

A wide variety of durations for HIPEC have been reported ranging from 30 to 120 min. The duration is not arbitrary and selection should proceed according to the pharmacologic clearance of the chemotherapeutic drug.

MACROMOLECULAR VEHICLES

In recent years an increased interest in macromolecular vehicles and other modulations of chemotherapeutic agents as a means of exploiting the regional dose intensity has emerged. The results of this research are conflicting. Contrary to intuitive thinking, macromolecules might penetrate more deeply in the subperitoneal space despite their lower diffusivities. The nature of the capillary permeability is probably the major factor responsible for this higher concentration in the subperitoneal space, together with an increased role of convection[91]. One should be cautious in concluding that this increased penetration into the subperitoneal space results in increased drug absorption into tumor nodules. That is, one should not assume that the neovascularity of tumor nodules has the same selectivity for macromolecules as normal capillaries[92]. A second obstacle to cancer chemotherapy penetration into tumor nodules concerns the interstitial pressures in tumor nodules; it is significantly higher than that of the surrounding tissue space[93]. Convection might reduce tumor penetration by macromolecules.

INDIVIDUAL DRUG SENSITIVITY OF TUMORS WITHOUT AND WITH HYPERTHERMIA

The selection of chemotherapeutic agents used in perioperative chemotherapy protocols has been based on research in chemotherapeutic responses in systemic administration, on pharmacodynamic and pharmacokinetic properties of the drug in intraperitoneal administration,

increased cytotoxicity with hyperthermia, and synergy between chemotherapeutic agents. There is solid evidence supporting a tumor-specific heterogeneous activity of cytotoxic drugs in cell cultures of different tumors[94,95].

Mahteme *et al*[96] recently stated the same heterogeneous cytotoxic response of cytotoxic drugs in PC samples in a variety of tumors. The clinical implication of these data justifies further research towards an individualized selection of drugs in PC patients. However, it should be acknowledged that as yet, there is no prospective data supporting an improved clinical outcome from drug selection based on *in-vitro* drug sensitivity testing.

BIDIRECTIONAL INTRAOPERATIVE CHEMOTHERAPY

The three-compartment model described above for peritoneal transport predicts transport by diffusion from the peritoneal compartment through a peritoneal and preperitoneal tissue layer to the plasma. Drugs move from the plasma compartment through the preperitoneal tissue layer to the peritoneal compartment. By combining intraoperative intravenous and intraoperative intraperitoneal cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer that contains the cancer nodules. This offers opportunities for optimizing cancer chemotherapy delivery to the target peritoneal tumor nodules. Elias *et al*[60] were the first to utilize this approach. Further pharmacologic studies are required to clarify the most effective chemotherapy agents for this bidirectional approach.

CONCLUSION

The administration of perioperative chemotherapy in patients with peritoneal carcinomatosis should be governed by pharmacological principles. Patients who have minimal residual disease as a result of cytoreductive surgery are candidates for perioperative chemotherapy by the intraperitoneal and intravenous route. Hyperthermia of the intraperitoneal chemotherapy solution will increase the cytotoxicity of the drug within the peritoneal cavity. In addition, heating of the peritoneal and preperitoneal tissues will maximize the systemic chemotherapy effects on carcinomatosis, a phenomenon known as heat targeting. Perioperative chemotherapy has become an important part of cancer treatment and should become a standard modality for prevention and treatment of a wide variety of cancers that involve the peritoneal surfaces.

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