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TOPIC HIGHLIGHT

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Pharmacology of cancer chemotherapy drugs for hyperthermic intraperitoneal peroperative chemotherapy in epithelial ovarian cancer

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Abstract

The peritoneal parietal and visceral surfaces of the abdomen and pelvis are an important anatomic site for the dissemination of epithelial ovarian cancer (EOC). The transcoelomic spread of cancer cells gives rise to peritoneal carcinomatosis (PC) which, without special treatments, is a fatal manifestation of EOC. In order to control PC cytoreductive surgery to remove macroscopic disease is combined with perioperative intraperitoneal (IP) and perioperative intravenous chemotherapy to eradicate microscopic residual disease. Chemotherapy agents are selected to be administered by the IP 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 is facilitated by moderate hyperthermia (41-42 ℃) of the IP chemotherapy solution. Timing of the chemotherapy as a planned part of the surgical procedure to maximize exposure of all peritoneal surfaces is crucial to success.

Key words: Intraperitoneal chemotherapy; Epithelial ovarian cancer; Ifosfamide; Cisplatin; Carboplatin; Taxanes; Pharmacokinetics; Pharmacodynamics

Core tip: Intraperitoneal (IP) chemotherapy is an important adjuvant treatment strategy in patients with advanced epithelial ovarian cancer. Although the clinical benefits have been demonstrated both in phase Ⅱ and Ⅲ trials, the pharmacologic rationale for this treatment strategy needs to be clarified. This manuscript reviews the pharmacokinetic and pharmacodynamic rationale of IP chemotherapy and analyzes the available data.

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INTRODUCTION

Epithelial ovarian cancer (EOC) is the second most common gynecologic malignancy. Worldwide in 2008, approximately 225000 women were diagnosed with EOC and 140000 died from their disease[1]. Seventy-five percent of these patients present with advanced disease outside of the pelvis at the time of diagnosis[2]. Besides the lymphatic and hematogenous routes of dissemination, transcoelomic spread of tumor cells is an acknowledged phenomenon

ultimately giving rise to peritoneal carcinomatosis (PC). In most patients, this intraperitoneal (IP) spread occurs before surgery as a direct consequence of full-thickness invasion of the involved organ by tumor and subsequently exfoliation of tumor cells in the peritoneal cavity. Alternatively, IP spread may be the result of surgical trauma that causes release of tumor cells from transected lymph and blood vessels and manipulation of the primary tumor. The combination of optimal cytoreductive surgery (CRS) and effective platinum-based chemotherapy has resulted in significant survival benefit for these women. Nevertheless five year survival for patients with International Federation of Gynecologists and Obstetrics stage ⅢC EOC only reaches 32.5%[3]. In an attempt to improve clinical results in EOC patients the IP route of chemotherapy administration has been explored both as an alternative and as an addition to systemic chemotherapy. This topic highlight manuscript aims to review the pharmacokinetic and pharmacodynamic data currently available regarding the IP delivery of cancer chemotherapy agents in patients with PC of ovarian origin. Pubmed was questioned with the search terms; EOC, peritoneal metastases, PC, IP chemotherapy, CRS, pharmacology, pharmacokinetics, pharmacodynamics. No exclusion criteria were used. Relevant English language articles were reviewed both in abstract and full text.

PERITONEAL PLASMA BARRIER

The rationale of administering chemotherapeutic drugs into the peritoneal cavity is based on the relative transport barrier which 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[4]. 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[5]. 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 may be its role as a first line of defense against PC[6]. Any disruption in the peritoneal lining facilitates the adhesion-invasion cascade of tumor cells, resulting in the development of peritoneal tumor nodules on the abdominal or pelvic surface[6,7].

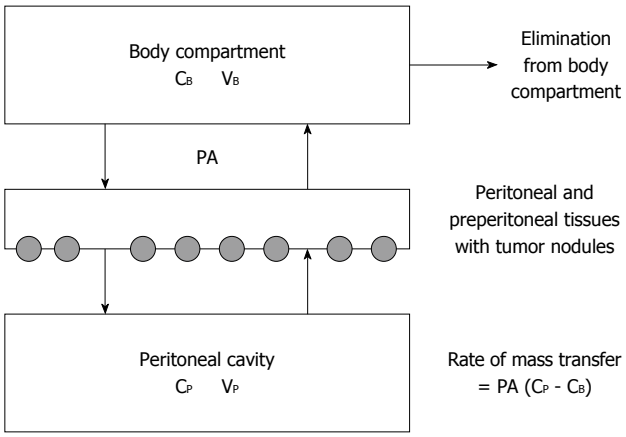

Figure 1 Three-compartment model of peritoneal transport in which transfer of a drug from the peritoneal cavity to the blood occurs across the peritoneal membrane and preperitoneal tissues. In these tissues the peritoneal surface cancer nodules are located. The permeability-area product (PA) governs 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. Modified from Dedrick *et al*[16].

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*[8] 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. Indirect evidence supporting this hypothesis in humans can be derived from the fact that the extent of the peritonectomy in PC patients does little to alter the IP chemotherapy pharmacokinetics of Mitomycin C or 5-fluorouracil[9,10]. Newer data suggest that major resections of visceral peritoneum increase the clearance of doxorubicin and mitomycin from peritoneal space[11,12]. Basic research rather demonstrates that not only the mesothelial lining but also the blood capillary wall and the surrounding interstitial matrix are the principal barrier for clearance of molecules from the abdominopelvic space[13].

Most basic research concerning the pharmacokinetic properties of the peritoneum is derived from the peritoneal dialysis literature[14]. 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 (Figure 1). This results in the following equation: Rate of mass transfer = permeability area (PA) [concentration in peritoneal cavity (C_P) - concentration in the blood (C_B)].

Although this offers a simple conceptional model of transport and states the importance of the effective exposure area, it only offers quantitative predictability once PA is empirically determined for each drug. It also does not offer insight into the actual tissue penetration at the level

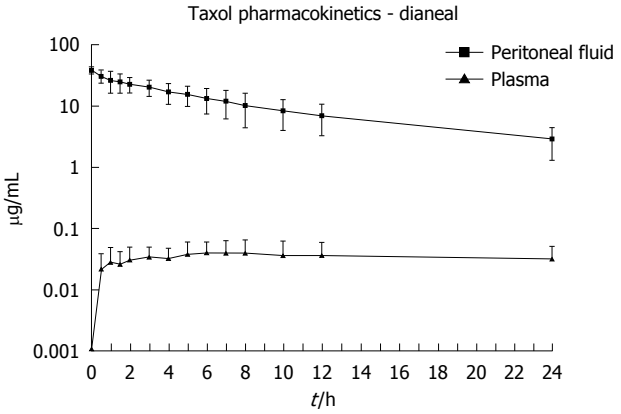

Figure 2 Pharmacokinetic study of concentration versus time for intraperitoneal paclitaxel. The chemotherapy agent at 30 mg/m^2 was instilled directly into the peritoneal cavity as rapidly as possible in a 1.5% dextrose peritoneal dialysis solution. The concentration of paclitaxel was determined in peritoneal fluid and in plasma for 24 h[51].

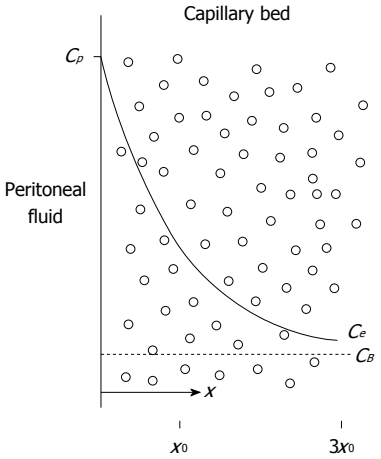

Figure 3 Conceptual diagram of tissue adjacent to the peritoneal cavity. Solid line shows the exponential decrease in the free tissue interstitial concentration, C_e, as the drug diffuses down the concentration gradient and is removed by loss to the blood perfusing the tissue. Also shown are the characteristic 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. C_P: The free drug concentration in the peritoneal fluid; C_B: The free drug concentration in the blood (or plasma). Modified from Dedrick *et al*[16].

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 PERI-OPERATIVE IP CANCER CHEMOTHERAPY

Pharmacokinetics explores what the body does to the cancer chemotherapy drug and pharmacodynamics explores what the drug does to the body. The IP route of delivering chemotherapy is logistically less convenient and technologically more challenging than conventional intravenous chemotherapy. This explains why the pharmacokinetic rationale of IP chemotherapy needs to be clarified to justify this route of cancer chemotherapy administration. IP administration of chemotherapeutic agents gives high response rates in PC patients because the peritoneal plasma barrier provides dose-intensive therapy. Based on peritoneal dialysis research, Dedrick *et al*[15] concluded that the peritoneal permeability of a number of hydrophilic anticancer drugs may be considerably less than the plasma clearance of that same drug. This results in a significantly higher concentration in the peritoneal cavity as compared to the plasma after IP administration. This concentration difference offers the opportunity of exposing the residual tumor cells after CRS 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 IP *vs* plasma exposure[14,15]. The marked increase in exposure of peritoneal surfaces to chemotherapy solution as compared to plasma is illustrated in Figure 2. The chemotherapy agent, paclitaxel has a high molecular weight (853.9 kDa) and is hydrophilic compound; consequently it is slow to cross the peritoneal cavity to plasma barrier. The AUC ratio is approximately 1000[12].

An important consideration is that high IP concentration or AUC IP/intravenous does not automatically confer a greater efficacy. Even with greatly elevated IP cancer chemotherapy concentrations, there may be limited penetration of the chemotherapeutic agent into the peritoneal tumor target. The ideal drug for IP chemotherapy has a high peritoneal tissue concentration as a result of direct IP administration and a high penetration into the cancer nodule[12]. This should occur along with slow diffusion through the capillary endothelium deep 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.

PHARMACODYNAMICS OF IP CHEMOTHERAPY

The efficacy of IP cancer chemotherapy protocols is governed by both non-pharmacokinetic variables (tumor nodule size, density, vascularity, interstitial fluid pressure, binding, temperature) and pharmacokinetic variables. As such, the simplified two-compartment model described above may not provide an adequate theoretical model for penetration of the intraoperatively administered (either intravenous or IP) chemotherapy into the peritoneal wall and into the tumor nodules. Dedrick *et al*[16,17] proposed a mathematical model seen in Figure 3 addressing the tissue penetration of low-molecular weight molecules. The drug diffuses from its peritoneal 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 calculated according to the formula: $C_e = C_B + (C_P - C_B) \exp[- (k/D)^{1/2}x]$.

Table 1 Pharmacokinetic and pharmacodynamic variables of perioperative cancer chemotherapy

Pharmacokinetic variables	Pharmacodynamic variables
Dose	Tumor nodule size
Volume	Density
Duration	Vascularity
Carrier solution	Interstitial fluid pressure
Pressure	Binding
Molecular weight	Temperature

In this formula (k/min) 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 an effective chemotherapy concentration is very limited and is in the order of 1-2 mm[18,19]. Ozols *et al*[20] confirmed adriamycin penetrating only 4-6 cell layers of tumor on the diaphragm in a rodent model of ovarian cancer. In all likelihood there is a variable penetration for each drug and type of tumor. This has important consequences for implementing perioperative chemotherapy in PC patients. Over the past 40 years; the designation of "optimal" CRS in EOC has evolved greatly from no residual disease > 1 cm to no gross residual disease[21]. Since the landmark study by Hoskins *et al*[22], there is a growing body of evidence supporting that patients with no gross residual disease have an important survival benefit[23-25]. In the Gynecologic Oncology Group trial patients with 0.1-1.0 cm and > 1.0 cm residual disease had an increased risk of recurrence (HR = 1.96, 95%CI: 1.70-2.26; and HR = 2.36, 95%CI: 2.04-2.73, respectively) and death (HR = 2.11, 95%CI: 1.78-2.49; $P < 0.001$; and HR = 2.47, 95%CI: 2.09-2.92, respectively) when compared to patients with no macroscopic residual disease[22]. In 3216 patients with EOC, du Bois *et al*[25] in a pooled analysis of three randomized controlled trials, after multivariate analysis demonstrated a statistically significant overall and progression-free survival benefit when complete resection was compared to patients with residual small (1-10 mm) tumor burden after surgery ($P < 0.001$).

Although the techniques of performing CRS in EOC have become more and more standardized, unfortunately the same cannot be said of the intraoperative and postoperative IP cancer chemotherapy regimens used in clinical practice today.

Table 1 summarizes all pharmacokinetic and pharmacodynamic variables involved in these various perioperative cancer chemotherapy protocols. One could state that the PK variables influence the amount of drug showing up at the level of the tumor nodule and that the PD variables subsequently determine what goes on inside the tumor nodule. As such the tumor nodule should be considered the most appropriate endpoint in the pharmacologic exploration regarding these treatment strategies. A much needed standardization of the IP cancer chemotherapy regimens should be based on both pharmacologic investigation at this level of the tumor nodule and further phase Ⅱ and Ⅲ clinical trials.

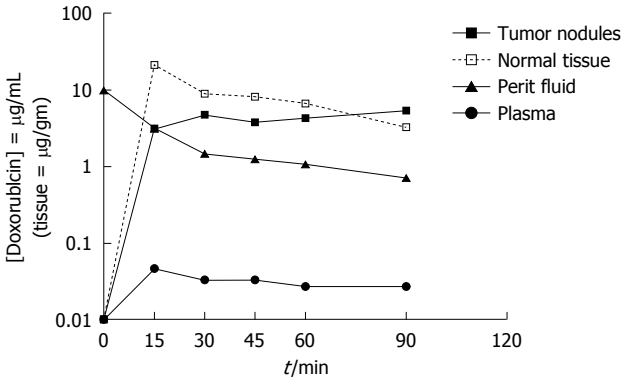

Figure 4 Doxorubicin levels in tumor nodules, normal adjacent tissues, peritoneal fluid and plasma during hyperthermic intraperitoneal perioperative chemotherapy over 90 min with 15 mg/m² doxorubicin intraperitoneal administration. Modified from Van der Speeten *et al*[32].

CYTOTOXIC DRUGS UNDER INVESTIGATION FOR IP ADMINSTRATION IN EOC

The number of reported variations in IP chemotherapy treatment protocols for EOC is extensive. All these variations reflect attempts to improve diffusivity D, decrease the rate constant K, permeability P or effective membrane area A.

Doxorubicin

Doxorubicin ($C_{27}H_{29}NO_{11}$) or hydroxyldaunorubicin (adriamycin) is an anthracycline antibiotic. Historically it has been categorized as a DNA-intercalating drug but experimental work suggests that interaction of doxorubicin with the cell surface membrane rather than its intracellular uptake is an essential first step for doxorubicin cytotoxity[26,27]. Because of its wide *in vitro* and *in vivo* activity against a broad range of malignancies, its slow clearance from the peritoneal compartment due to the high molecular weight of the hydrochloride salt (579.99 kDa), its favorable AUC ratio of IP to intravenous concentration times of 230, and the absence of risk for dose-limiting cardiotoxicity when used intraperitoneally; doxorubicin was considered a potential beneficial agent for perioperative IP delivery in EOC. This was supported by both experimental and clinical pharmacokinetic data[20,28-32]. Figure 4 shows the pharmacologic profile of intraperitoneally administered doxorubicin[32]. The consistent finding of doxorubicin sequestration in tumor nodules raises questions about the possible underlying mechanism. Simple diffusion, forces as proposed by Dedrick and Flessner are not enough to explain the phenomenon. In the absence of experimental data supporting active transport of cancer chemotherapy drugs over membranes the authors postulate active binding to the cell membrane as

a possible mechanism. The sequestration phenomenon of doxorubicin in tumor nodules is a constant one in its presence regardless the underlying pathology or subtype. A consequence is that the cancer chemotherapy levels measured in the tumor nodules may be more important than considered in the past.

Cisplatin

Cisplatin (cis-diamminedichloroplatinum-Ⅲ, CDDP) causes apoptotic cell death by formation of DNA adducts[33]. It has been well studied in the setting of adjuvant normothermic postoperative IP chemotherapy of residual small volume ovarian cancer after CRS. Three randomized trials showed a significant survival benefit[34-36]. In the setting of CRS and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC), cisplatin has been used for intracavitary therapy of ovarian cancer in several phase Ⅱ studies[37,38]. Currently three randomized phase Ⅲ studies are recruiting patients to determine the role of CRS + HIPEC in primary and recurrent EOC. Schem *et al*[39] showed an excellent *in vitro* and *in vivo* thermal augmentation of cisplatin. The penetration of cisplatin into tumor nodules was studied by several groups. Los *et al*[40] for the first time described intratumoral distribution of cisplatin after IP administration and suggested that the advantage over IP *vs* IV administration was maximal in the first 1.5 mm. van de Vaart *et al*[41] investigated the cisplatin induced DNA adduct formation and could measure this 3-5 mm into the tumor tissue. Esquis *et al*[42] in an experimental model reported an enhanced cisplatin penetration when cisplatin was administered with increased pressure.

Carboplatin

Carboplatin [(1,1-cyclobutanedicarboxylato)platinum(II)] is a higher molecular weight platinum compound than cisplatin. Its main advantage is its decreased renal toxicity. As such it is currently explored in normothermic IP chemotherapy protocols in patients with advanced ovarian cancer[43,44]. Czejka *et al*[45] in a clinical study with normothermic carboplatin reported a relative bioavailability (calculated as AUC-values) which was at least 6 times higher in the IP fluid than in the serum for 48 h. Los *et al*[19] compared carboplatin and cisplatin after IP administration in a rat model of PC. Their data demonstrate that despite a clear pharmacokinetic advantage of IP carboplatin over cisplatin; its capacity to penetrate into peritoneal cancer nodules and tumor cells is far lower than that of cisplatin. These data limit have limited clinical its application in the past. In contrast, a more recent direct comparison reveals a comparable or better drug penetration of IP carboplatin when compared to IP cisplatin given at equitoxic doses[46]. This has recently revived clinical interest in its IP application.

Taxanes

Paclitaxel and docetaxel are taxanes considered for IP chemotherapy. The taxanes stabilize the microtubule against depolymerization; thereby disrupting normal microtubule dynamics[47]. They exert cytotoxic activity against a broad range of tumors. Due to their high molecular weight these molecules have a remarkable high AUC ratio of respectively 853 and 861[48]. This translates itself into a clear pharmacokinetic advantage for IP administration[49]. The data regarding possible thermal augmentation of taxanes are conflicting[50-53]. Taxanes have been used in a neoadjuvant IP setting as well as intraoperatively and postoperatively. Their cell-cycle specific mechanism of action makes them a particular good candidate for repetitive application such as in normothermic adjuvant postoperative IP chemotherapy[34,35]. Novel formulations of taxanes aiming at an increased bioavailability are under investigation for IP administration during HIPEC[54].

ROLE OF HYPERTHERMIA

Adding hyperthermia to IP chemotherapy may increase tumor response to cancer chemotherapy through several mechanisms. First, heat alone has a direct anti-tumor effect. Mild hyperthermia above 41 ℃ induces selective cytotoxicity of malignant cells by several mechanisms: impaired DNA repair, protein denaturation and, inhibition of oxidative metabolism in the microenvironment of malignant cells. This leads to increased acidity, lysosomal activation and, increased apoptotic cell death[55-57]. In this setting, thermal tolerance can be induced by up regulation of heat shock proteins, which may limit the importance of a direct anti-tumor effect of heat[58]. Second, applying mild hyperthermia augments the cytotoxic effects of some chemotherapeutic agents. Synergy between heat and cancer chemotherapy drugs may arise from multiple events such as heat damage to ABC transporters (drug accumulation), intra-cellular drug detoxification pathways and, to repair mechanisms of drug-induced DNA adducts[59]. Such augmented effects are postulated for doxorubicin, platinum complexes, mitomycin C, melphalan, docetaxel, irinotecan and, gemcitabine[28,59-64]. Third, hyperthermia may increase the penetration depth of the cancer chemotherapy solution into tissues and tumor nodules. Jacquet *et al*[28] report tissue penetration of doxorubicin is enhanced when the cancer chemotherapy solution is administered intraperitoneally at 43 ℃. In addition, hyperthermia does not affect the pharmacokinetic advantages of IP doxorubicin with low plasma and distant tissue levels.

The elevated interstitial fluid pressure in tumor nodules, compared to normal tissue, is an acknowledged phenomenon[65]. Furthermore, in experimental tumors with a single nodule, interstitial fluid pressure is relatively uniform in the nodule and drops precipitously in the periphery at the tumor-normal tissue interface[66]. Furthermore, Leunig e*t al*[67] report a thermal dose-dependent decrease in interstitial fluid pressure in experimental solid tumors in an animal model after hyperthermia. All this experimental data however could not establish a direct effect of hyperthermia on survival. Klaver *et al*[68] in a rat model of PSM for first time separated the intraoperative IP chemo-

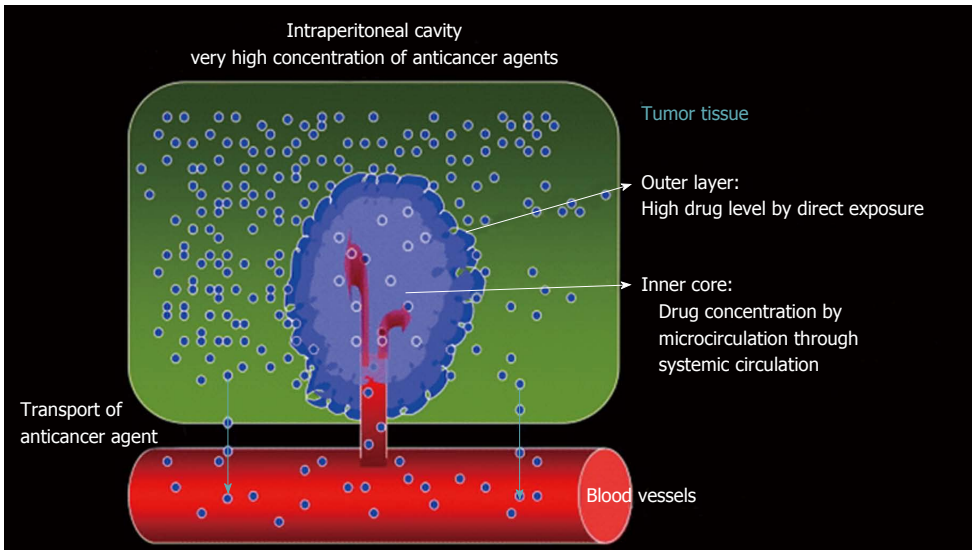

Figure 5 Pharmacologic concept of bidirectional intravenous and intraperitoneal chemotherapy. Modified from Fujiwara *et al*[69].

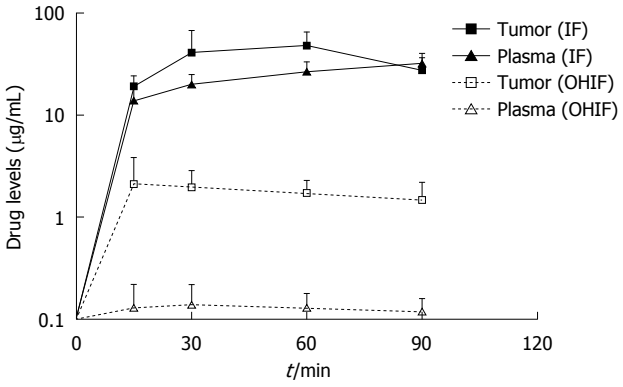

Figure 6 Comparison of ifosfamide and 4-hydroxyifosfamide concentrations in tumor nodules and in plasma during bidirectional intraoperative chemotherapy. OHIF: 4-OH-ifosfamide.

therapy from the IP hyperthermia. They demonstrated that the survival of the PC rats after CRS was highly dependent on the presence of the chemotherapeutic agent in the perfusate but not on the hyperthermia. No similar human data are available at this point in time.

BIDIRECTIONAL INTRAOPERATIVE CHEMOTHERAPY: RATIONALE AND PHARMACOLOGIC DATA

The Dedrick-model for peritoneal transport predicts transport by diffusion from the peritoneal compartment through a peritoneal and preperitoneal tissue layer to the plasma and, vice versa[15]. Figure 5 demonstrated that through combining intraoperative intravenous and intraoperative IP cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer containing the cancer nodules[69]. Chemotherapy from both the IP and intravenous compartments converges on the tissues at the interface of peritoneal space and peritoneal surface where the tumor nodules reside. Elias *et al*[70] first reported the clinical use of intraoperative intravenous 5-fluorouracil and leucovorin in conjunction with oxaliplatin-based hyperthermic IP perioperative chemotherapy in patients with PC of colorectal origin. More recently our group reported a similar effort in ovarian cancer with intravenous intraoperative ifosfamide[71]. The treatment strategy that has been employed in our studies is very similar to that published by Zylberberg *et al*[72] for ovarian cancer. His study showed excellent clinical results when systemic ifosfamide infusion was combined with IP cisplatin. We modified his ifosfamide regimen using an infusion over 90 min in the operating room. We demonstrated consistent high levels of ifosfamide and its active metabolite 4-OH-ifosfamide throughout and after the 90-min infusion in the peritoneal tumor nodules without increasing its systemic toxicity (Figure 6). This created a pharmacologically advantageous situation where a normothermic administered IV drug became subject to the effect of the local hyperthermia in the peritoneal fluid and tumor nodule. Timing of intravenous chemotherapy (intraoperative *vs* postoperative) is not pharmacokinetically neutral and as such emerges as a new pharmacokinetic variable.

TIMING OF IP CANCER CHEMOTHERAPY IN RELATION TO TIMING OF CRS

In the clinical application of IP chemotherapy in EOC patients, intervention can occur at four points in the timeline.

Induction IP and/or intravenous chemotherapy

Induction IP and/or intravenous Chemotherapy is suggested as an option for reducing dissemination to the extra-abdominal space, testing the tumor biology and, for reducing the extent of small PC nodules and, theoreti-

cally this approach, called neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy[73]. Radiological and clinical responses with NIPS have been reported by several groups[74-76]. However, although NIPS may reduce the tumor load to be addressed by CRS, it has several disadvantages. Adhesions from prior surgical interventions may interfere with adequate IP drug distribution and, as complete responses are unusual, further cytoreduction-chemotherapy is necessary if the approach is to be curative. NIPS is reported to add to morbidity and mortality of further surgical treatment and, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible to assess[77].

Early postoperative intraperitoneal chemotherapy

Early postoperative intraperitoneal chemotherapy (EPIC) has some conceptual advantages. It is administered after CRS at the time of minimal residual tumor burden and, IP treatments initiated before wound healing occurs can minimize non-uniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits. The proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell-cycle specific drugs such as the taxanes. Most EPIC regimens are administered postoperatively (day 1 to day 4/5) through both an inflow catheter and outflow drains inserted at the time of CRS and, can be applied with or without HIPEC[78].

Long-term combined IP and systemic chemotherapy

Several phase Ⅲ trials demonstrated that intravenous plus IP chemotherapy improves survival in patients with optimally debulked stage Ⅲ ovarian cancer, compared to intravenous chemotherapy alone[34-36,69]. Some of these studies report a significant number of catheter-related problems and inability of the patient to complete the intended number of chemotherapy cycles This approach may alsobe 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.

HIPEC

HIPEC has been explored in more than 40 studies in EOC. Unfortunately, most of these trials are small in number (< 50 patients) and have broad entry criteria[79]. Four randomized trials (NCT00426257, NCT01376752, NCT01539785 and NCT01091636) are currently exploring the role of HIPEC in the treatment of EOC. Failure analysis for CRS in EOC patients indicates recurrent cancer occurs most frequently within the abdominal and pelvic cavity. Although systemic metastases occur, treatment failures rarely occur in liver, lungs or, other systemic sites. In order to optimize the treatment of patients with PC, the greatest benefit will probably result from a combination of the four treatment strategies.

CONTROVERSIES AND FUTURE DIRECTIONS

Despite a growing evidence supporting the role of IP chemotherapy in the treatment of EOC, important controversies and questions remain to be answered. As the initial trials with IP chemotherapy in EOC were combined intravenous-IP chemotherapy regimens, some authors designate the observed effect to being the result of the dose density of the regimen, rather than the effect of the IP chemotherapy. Also, the current weekly schedules of intravenous taxanes as in JGOG 3016, MITO 7, GOG 0262 and ICON 8 have further raised the bar[80,81]. These improvements in systemic chemotherapy however do not annihilate the pharmacologic and clinical data supporting the superiority of a combined intravenous-IP approach. High grade EOC is characterized by an important overexpression of vascular endothelial growth factor (VEGF). As a logical consequence VEGF inhibitors as bevacuzimab are under investigation, both by the intravenous and IP route[82-84].

CONCLUSION

The administration of perioperative IP chemotherapy in EOC patients with PC should be governed by pharmacologic principles. Patients who have minimal residual disease as a result of optimal CRS are candidates for perioperative chemotherapy by the IP and intravenous route. Hyperthermia of the IP chemotherapy solution might increase the cytotoxicity of the drug within the peritoneal cavity. Heating of the peritoneal and preperitoneal tissues will maximize the systemic chemotherapy effects on carcinomatosis, a phenomenon known as heat targeting. IP chemotherapy has become an important part of EOC 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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