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Drugs, doses, and durations of intraperitoneal chemotherapy: standardizing HIPEC and EPIC for colorectal, appendiceal, gastric, ovarian peritoneal surface malignancies and peritoneal mesothelioma.

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Drugs, doses, and durations of intraperitoneal chemotherapy: standardizing HIPEC and EPIC for colorectal, appendiceal, gastric, ovarian peritoneal surface malignancies and peritoneal mesothelioma.

Peritoneal surface malignancy (PSM) is a common manifestation of digestive and gynecologic malignancies alike. At present, patients with isolated PSM are treated with a combination therapy of cytoreductive surgery (CRS) and hyperthermic peroperative intraperitoneal chemotherapy (HIPEC). The combination of CRS and intraperitoneal (IP) chemotherapy should now be considered standard of care for PSM from appendiceal epithelial cancers, colorectal cancer and peritoneal mesothelioma. Although there is a near universal standardization regarding the CRS, we are still lacking a much-needed standardization amongst the various IP chemotherapy treatment modalities used today in clinical practice. Pharmacologic evidence should be generated to answer important questions raised by the myriad of variables associated with IP chemotherapy.

Keywords: Peritoneal Surface Malignancy, HIPEC, EPIC, BIC

Introduction

Peritoneal surface malignancy (PSM) is a common manifestation of digestive and gynecologic malignancies alike. At present, patients with isolated PSM are treated with a combination therapy of cytoreductive surgery (CRS) and hyperthermic peroperative intraperitoneal chemotherapy (HIPEC) [1]. CRS and HIPEC have evolved over three decades and have demonstrated encouraging clinical results in several phase II and III trials [2-10]. The combined treatment modality should now be considered standard of care for PSM from appendiceal epithelial cancers, colorectal cancer and peritoneal mesothelioma [11-13]. Promising results have also been published for HIPEC in ovarian cancer and gastric cancer [5, 9, 14]. Although there is now a clearly defined standardization of CRS, based on the work by Sugarbaker *et al*. [15, 16], no standardized intraperitoneal (IP) chemotherapy treatment modalities exist. Variables to

be considered are: normothermic versus hyperthermic IP chemotherapy, open versus closed HIPEC technique, but also the use of HIPEC with or without early postoperative intraperitoneal chemotherapy (EPIC) or the sole administration of EPIC. This also implicates the important pharmacologic variables associated with the chemotherapy agents that are currently available for the administration of HIPEC [17] and EPIC [18]. There is a pressing need to generate pharmacologic data working towards standardization amongst the myriad of IP treatment protocols currently applied.

Pharmacology of IP chemotherapy can be artificially divided between pharmacokinetics and pharmacodynamics. Whereas pharmacokinetics describes what the body does to the drug, pharmacodynamics looks at what the drug does to the body. Pharmacokinetics of IP chemotherapy studies the alterations between the moment of administration of the IP chemotherapy and the cancer chemotherapy drug showing up at the level of the tumor nodule. Important pharmacokinetic variables include drug dose, volume, duration, carrier solution, pressure and molecular weight. The basic way of depicting pharmacokinetic data is by a concentrations x time graph. Pharmacodynamics subsequently looks into the effect of that cancer chemotherapy drug on the tumor, considering tumor nodule size, density, vascularity, interstitial fluid pressure, binding and temperature. Pharmacodynamic data are depicted in a concentrations x effect graph.

In this manuscript, we review current data regarding drugs, doses, and durations of treatments of IP chemotherapy: standardizing HIPEC and EPIC for colorectal, appendiceal, gastric, ovarian PSM and peritoneal mesothelioma.

Selection of chemotherapy drugs for IP administration

Perhaps the most crucial aspect of an optimal IP chemotherapy treatment modality is the selection of a chemotherapy drug for use within the peritoneal space. The ideal drug for IP chemotherapy has a high peritoneal tissue concentration; because

of direct IP administration, and a high penetration into the cancer nodule. This should occur in conjunction with slow diffusion of the chemotherapy solution through the peritoneal membrane and deep in the subperitoneal space, resulting in low systemic exposure. The area-under-the-curve (AUC) ratio IP/IV is important in that it quantifies the dose intensity expected in the treatment of PSM. Table 1 summarizes the pharmacologic properties of the chemotherapy drugs most frequently selected for IP application [19]. Pharmacologic variables that should be taken into account are the route of administration, either IP only or IP combined with intravenous (IV) administration, (bidirectional intraoperative chemotherapy (BIC)). The use of naked drugs versus nanoparticles and single drugs versus multiple drugs should also be considered. To select a chemotherapy drug one must know the response expected with this drug in patients with metastatic disease. This emphasizes the increasing importance of chemosensitivity testing, towards a patients-tailored approach of selecting the ideal drug for IP and/or IV administration. At present several preclinical work has been conducted in this field using a wide variety of *in vitro, in vivo* and *ex vivo* assays using several patient-derived tumor cell-lines in combination with several chemotherapy agents [20, 21]. However, important to note is that during the *in vitro* assays, the 3-D structure of the tumors and hence the important pharmacodynamics of the nodules are lost. Moreover, metabolisation which is very important for the cytotoxic effect of several drugs is not taking in to account. *Ex vivo* assays using patient-derived xenografts and orthotopic animal models also present an impaired view of the clinical situation. For example, implantation of tumor cells subcutaneously, due to differences in microenvironment, will result in the formation of one tumor nodule which fails to progress and metastasize. Further research, and careful validation of such assays are needed, taking into account the heterogeneity of tumors and the important

pharmacodynamic variables. In the present era of omics assays, gene expression profiling has gained increasing interest in clinical applications to predict oncologic outcomes. Levine *et al*. analyzed gene expression profiles of appendiceal and colorectal PSM samples from patients undergoing HIPEC after complete CRS. They reported distinct genomic signatures for colorectal PSM when compared to appendiceal PSM. Three distinct phenotypes, two consisting of predominantly appendiceal samples (low-risk appendiceal and high-risk appendiceal) and the third with predominately primary colorectal samples (high-risk colorectal), were identified. Furthermore, overall survival (120 months) after optimal CRS and HIPEC was significantly different between the low-risk appendiceal and the high-risk colorectal group [22]. Fujishima *et al*. used immunohistochemistry to evaluate mucin (MUC) protein expression in tumor nodules of patients with peritoneal dissemination from colorectal cancer as the only synchronous distant metastasis, who had received HIPEC. They report that in patients positive for MUC2 expression the 3-year overall survival rate was 0.0%, whereas in patients negative for MUC2 expression, the 3-year overall survival rate was 61.1% [23]. This emphasizes the importance of omics assays to help define better candidates for certain therapies and possibly, in the near future, the choice of chemotherapeutic agents.

Dosimetry of IP chemotherapy

The current dosing regimens of IP chemotherapy can be divided into body surface area (BSA)-based and concentration-based. Most groups use a drug dose based on calculated BSA (mg/m2) in analogy to systemic chemotherapy regimens. These regimens take BSA as a measure for the effective peritoneal contact area, the peritoneal surface area in the Dedrick formula [24]. The Dedrick formula on itself is an application of Fick's law of diffusion. Rubin *et al*. [25] however, demonstrated there is an imperfect correlation between actual peritoneal surface area and calculated BSA. There may also

be sex differences in peritoneal surface areas, which in turn affects absorption characteristics. BSA-based IP chemotherapy will result in a fixed dose (BSA-based) diluted in varying volumes of perfusate; i.e.; different concentrations depending on substantial differences in the body composition of patients and differences in the HIPEC technique (open versus closed abdomen). From the Dedrick formula we know that peritoneal concentration and not peritoneal dose is the driving diffusion force [24]. The importance of this has been discussed by Elias *et al.* [26] in a clinical investigation where 2-, 4- , and 6-liters of chemotherapy solution was administered with a constant dose of chemotherapy solution. A more dilute IP chemotherapy concentration retarded the clearance of chemotherapy and resulted in less systemic toxicity [27]. Therefore, it can be assumed that by the diffusion model, less concentrated chemotherapy would penetrate to a lesser extent into the cancer nodules and normal tissues. On the other hand, concentration-based chemotherapy offers a more predictable exposure of the tumor nodules to the IP chemotherapy and thus efficacy [28]. Unfortunately, the prize to be paid for a better prediction of the efficacy of the IP chemotherapy is a high unpredictability of the plasmatic cancer chemotherapy levels and thus toxicity. Indeed, according to the Dedrick formula of transport over the peritoneal membrane, an increase in the volume of concentration-based IP chemotherapy solution will cause an increase in both diffusion surface and the amount of drug transferred from peritoneal space to plasma [29]. Currently, there is an ongoing study at our hospital evaluating both the pharmacology and morbidity of the different dosing regimens; entitled 'concentration-based versus body surface area-based peroperative intraperitoneal chemotherapy after optimal cytoreductive surgery in colorectal peritoneal carcinomatosis treatment: randomized non-blinded phase III clinical trial (COBOX trial)' (https://clinicaltrials.gov/ct2/show/NCT03028155?term=NCT03028155&rank=1).   In

this pilot study, pharmacologic parameters, the AUC ratio IP/IV and the concentrations in the tumor nodules will be correlated with 3-month overall morbidity and mortality, calculated using the Dindo-Clavien classification. Secondary endpoint is the overall 1-year survival.

Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)

HIPEC is the most widely explored modality that has consistent clinically improved outcomes in many phase II and III trials [2, 3, 30-39]. The drugs that are used in this setting are non cell-cycle specific drugs, which make them applicable for single instillation as in HIPEC (Table 2) [17].

Cisplatin

Cisplatin (cis-diamminedichloroplatinum-III, CDDP) is an alkylating agent that causes apoptotic cell death by formation of DNA adducts [40]. Both normothermic and hyperthermic IP application have been explored in the treatment of ovarian cancer, gastric cancer, and peritoneal mesothelioma [4, 17, 41-46]. It is eliminated by renal excretion and consequently the main concern with its use is renal toxicity [47]. Urano *et al*. showed an excellent in vitro and in vivo thermal augmentation of cisplatin [48]. Current applied cisplatin-based HIPEC regimens are the 'Sugarbaker Regimen'[49] and the 'National Cancer Institute Milan Regimen'[50].

Oxaliplatin

Oxaliplatin (oxalato-1,2-diaminocyclohexane-platinum(II)) is a third generation platinum complex with proven cytotoxicity in colon and appendiceal neoplasms [51]. In a dose escalation and pharmacokinetic study, Elias *et al*. demonstrated that 460 mg/m² of oxaliplatin in 2L/m² of chemotherapy solution over 30 minutes was well tolerated [32, 52]. The low AUC ratio is compensated by the rapid absorption of the drug into the

tissue, being the reason for the short application time. Oxaliplatin is subject to substantial heath augmentation [48, 53]. In a phase I trial, Elias *et al*. evaluated the pharmacokinetics of heated IP oxaliplatin administered in increasingly hypotonic solutions of 5% dextrose [54]. This trial was based on earlier published experimental data that IP hypotonic solutions increase platinum accumulation in tumor cells [55]. They reported that oxaliplatin clearance from the IP cavity was similar regardless of the osmolarity, but that very hypotonic solutions induce high incidence of IP hemorrhage and thrombocytopenia. As a result of high incidence hemorrhagic complications in another prospective multicenter trial organized by Pomel *et al*., the dose of oxaliplatin was reduced to 350 mg/m^2. However, the incidence of the hemorrhagic complications (29%) did not decrease and the trial was closed prematurely [56]. Chalret du Rieu *et al*. performed a population pharmacokinetics study, including 75 patients, treated with CRS and oxaliplatin-based HIPEC [57]. They report grade 3/4 thrombocytopenia in 14% of treated patients. Moreover, they concluded that the higher the absorbed dose from the peritoneal cavity, highly dependent on the initial oxaliplatin concentration, the deeper the resultant thrombocytopenia. In an analysis of 701 patients treated with CRS and HIPEC with oxaliplatin or other chemotherapeutic agents, Charrier *et al*. reported that oxaliplatin-based HIPEC increased the risk of hemorrhagic complications compared to other drugs [58]. In contrast to cisplatin and mitomycin, oxaliplatin traditionally is considered not stable in chloride-containing solutions. This necessitates a dextrose-based carrier which may result in serious electrolyte disturbances and hyperglycemia during the intracavitary therapy [59]. Unknown to most this degradation of oxaliplatin in normal saline only accounts for less than 10% of the total amount at 30 minutes; as when applied during HIPEC. Moreover, oxaliplatin degradation was associated with the formation of its active drug form [Pt(dach)Cl$_2$] [60, 61]. Different oxaliplatin-based

HIPEC regimens are used in current clinical practice: 'Elias High Dose Oxaliplatin Regimen'[32], 'Glehen Medium Dose Oxaliplatin Regimen' and the 'Wake Forest University Oxaliplatin Regimen'[51].

Mitomycin C

Mitomycin C is an alkylating tumor antibiotic extracted from Streptomyces species which most important mechanism of action is through DNA cross-linking. Although mitomycin C is not regarded as a prodrug, it is not active against cancerous tissue as the unchanged molecule. The drug is modified as it enters the cell into an active state [62]. It is inactivated by microsomal enzymes in the liver and is metabolized in the spleen and kidneys. Jacquet *et al*. reported a clear pharmacokinetic advantage after IP administration with an AUC IP/IV ratio of 23.5 [63]. It is used for PC from colorectal cancer, appendiceal cancer, ovarian cancer, gastric cancer and, for diffuse malignant peritoneal mesothelioma both as HIPEC and EPIC [2, 3, 29, 63-66]. Barlogie *et al*. suggested *in vitro* thermal enhancement of mitomycin C [67, 68]. Our pharmacokinetic data in 145 HIPEC patients suggest that the largest proportion (62%) of the total drug administered remained in the body at 90 minutes [29]. This is in line with similar findings by Jacquet *et al*. and Van Ruth *et al*. [63, 69]. The location and chemical state of this large amount of retained mitomycin C remains to be determined. Controversies still exist regarding the proper dosimetry of the chemotherapy solution. Triple dosing regimen may results in more stable peritoneal levels of the drug throughout the time of IP chemotherapy. Current applied HIPEC dosing regimens are the 'Sugarbaker Regimen'[29], The 'Duth High Dose Mitomcyin C Regimen: Triple Dosing Regimen'[70] and the 'American Society of Peritoneal Surface Malignancy Low Dose Mitomycin C Regimen: Concentration-based Regimen'[71].

Doxorubicin

Doxorubicin or hydroxyldaunorubicin (adriamycin) is an anthracycline antibiotic. Initial research categorized it as a DNA-intercalating drug. It was later demonstrated that the actual mechanism of action is a temperature-dependent interaction of doxorubicin with the cell surface membrane [72-74]. Doxorubicin was considered a candidate for IP application based on 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, its favorable AUC ratio of IP to IV concentration times of 230 [17, 75-79]. The dose-limiting cardiotoxicity, which is the results of repeated dosing, when administered IV can also be avoided. Pilati *et al.* suggested a mild hyperthermic augmentation based on increased drug uptake and sensitization of tumor cells (but not normal mucosal cells) to the cytotoxic effects of doxorubicin [80, 81]. More recently PEGylated liposomal doxorubicin has generated interest for HIPEC application due to its favorable pharmacokinetics [82, 83]. Doxorubicin-based HIPEC has been used in PSM from appendiceal, gastric, ovarian and colon cancer, as well as in peritoneal mesothelioma [4, 84-86].

Bidirectional Intraoperative Chemotherapy (BIC)

By combining intraoperative IV and intraoperative IP cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer containing the cancer nodules (Figure 1). In 2002, Elias *et al.* first reported the clinical use of intraoperative IV 5-fluorouracil and leucovorin in conjunction with oxaliplatin-based HIPEC, to potentiate the effect of oxaliplatin (41). We also reported a clear pharmacokinetic advantage for the intraoperative IV administration of 5-fluorouracil

[87]. A similar pharmacokinetic advantage and heat targeting of intraoperative IV ifosfamide was demonstrated [49]. Ifosfamide is a prodrug that needs the cytochrome P450 system of liver or red blood cells to be activated to its active metabolite 4-hydroxyifosfamide. Consequently, it requires IV administration rather than IP instillation for its cytotoxic activity. The drug also shows true heat synergy. It may be an ideal systemic drug to increase the cytotoxicity of HIPEC. Most current protocols advocate bidirectional intraoperative chemotherapy (BIC) (Table 2). The bidirectional approach offers the possibility of optimizing cancer chemotherapy delivery to the target peritoneal tumor nodules. Further pharmacologic studies are needed to clarify the most efficient method of administration (continuous, bolus or, repeated bolus), doses and, choice of cancer chemotherapy drugs for this bidirectional approach.

Early Postoperative Intraperitoneal Chemotherapy (EPIC)

EPIC has some conceptual advantages. It is administered shortly after CRS at the time of minimal residual tumor burden. Moreover, IP treatments initiated before wound healing occurs can minimize non-uniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits. Disadvantages associated with EPIC are the increased risks of infection and postoperative complications [33, 88-90]. EPIC does not involve hyperthermia and is administered postoperatively (typically 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 [18]. Proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell-cycle specific drugs such as 5-fluorouracil and the taxanes (Table 3) [17, 91]. This implies administrating multiple cycles, each with a dwell time of around 23 hours before renewal. This ensures that all the residual tumor cells are susceptible for the cell cycle specific drug.

5-fluorouracil

The fluorinated pyrimidines have been successfully used for a wide variety of tumors and, are still an essential component of all successful gastrointestinal cancer chemotherapy regimens [92, 93]. This thymidylate synthase inhibitor binds covalently with the enzyme and prevents the formation of thymidine monophosphate, the DNA nucleoside precursor. Also, 5-FU by its metabolites 5-fluoro-uridine diphosphate and 5-fluoro-uridine triphosphate gets incorporated in RNA, resulting in a second cytotoxic pathway. The action of 5-fluorouracil is therefore cell cycle specific. These characteristics limit the use of IP 5-fluorouracil to EPIC [18, 94-97]. Minor augmentation of 5-fluorouracil by mild hyperthermia is reported [63]. 5-fluorouracil is not chemically compatible with other drugs in a mixed solution for infusion or instillation. The current regimens for EPIC with 5-fluorouracil are presented in Table 3.

Taxanes

Paclitaxel and docetaxel, with their high molecular weight these molecules, have a remarkable high AUC ratio of respectively 853 and 861 [19]. The taxanes stabilize the microtubule against depolymerization; thereby disrupting normal microtubule dynamics [98]. There is evidence supporting additional mechanisms of action [99]. They exert cytotoxic activity against a broad range of tumors. This translates itself into a clear pharmacokinetic advantage for IP administration [100]. The data regarding possible thermal augmentation of taxanes are conflicting [99]. Taxanes have been used in a neoadjuvant intraperitoneal (NIPS) setting as well as intraoperatively and postoperatively. Their cell-cycle specific mechanism of action makes them a better candidate for repetitive application such as in EPIC, NIPS or normothermic adjuvant postoperative IP chemotherapy. Novel formulations of taxanes aiming at an increased

bioavailability are under investigation [101]. The current regimens for EPIC with paclitaxel are presented in Table 3.

Monoclonal antibodies and avastin

Angiogenesis, the growth of new blood vessels from pre-existing vessels, is paramount for tumor growth and the formation of metastases. It is induced through the production of angiogenic factors by tumor cells [102, 103]. A key player in this process is vascular endothelial growth factor-A (VEGF-A), which binds to its receptors VEGFR-1 and VEGFR-2 and thereby increases endothelial cell survival, proliferation, migration and differentiation [104, 105]. At present, several targeted molecular therapies are introduced in the treatment of PSM. One of these therapies includes the use of bevacizumab (avastin), a recombinant humanized monoclonal antibody that blocks the activity of VEGF-A. Preclinical work performed by Gremonprez *et al*. showed that pretreatment with bevacizumab leads to a significantly lower interstitial fluid pressure in the tumor nodule, which may allow deeper penetration of the IP administered chemotherapeutic agent and higher drug concentrations in the tumor [106]. Several clinical studies have already evaluated the efficacy of IV bevacizumab combined with different chemotherapeutic agents; such as 5-fluorouracil, capecitabine, irinotecan, oxaliplatin, cisplatin and paclitaxel, for the treatment of colorectal and ovarian peritoneal malignancy/ascites [107-112]. It significantly increases the response rate and overall survival for these patients. A recent study, the BEV-IP trial (https://www.clinicaltrials.gov/ct2/show/NCT02399410?term=BEV-IP&rank=1),

initiated by Willaert *et al*., is the first prospective trial that will assess the safety and efficacy of IV bevacizumab followed by CRS and oxaliplatin-based IP chemotherapy in patients diagnosed with synchronous of metachronous colorectal PSM [113]. Attempts have also been made to investigate the potential use of IP bevacizumab as a curative

agent. Passot *et al*. and Chia *et al*. investigated the IP levels of VEGF at various time points during and after surgery [114, 115]. They report that VEGF is present in the peritoneal cavity of patients with PSM treated with curative intent, and its levels increase after CRS. Neoadjuvant bevacizumab significantly decreased the preoperative IP VEGF levels. However, neoadjuvant IV bevacizumab was associated with increased major morbidity [116]. They concluded that the use of preoperative IP bevacizumab for patients with extensive disease burden should be considered, especially in colorectal PSM. Other targeted molecular therapies include the use of drugs that inhibit the endothelial growth factor receptor (EGFR)-related factors to control tumor cell proliferation and differentiation. These drugs include cetuximab and panitumumab [117, 118].

Future directions in IP chemotherapy

Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

Neoadjuvant bidirectional chemotherapy uses both the IP and IV routes of chemotherapy administration prior to the CRS. It has been 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. Theoretically this approach, called neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy [119]. Radiological and clinical responses with NIPS have been reported by several groups [119-122]. 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 [123]. Furthermore, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible.

Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel approach to deliver IP chemotherapy to patients diagnosed with PSM [124]. During PIPAC, a normothermic capnoperitoneum (pressure of 12 mmHg) is established through a laparoscopic access in an operating room equipped with a laminar airflow. A cytotoxic solution is nebulized into the abdominal cavity during 30 minutes and thereafter removed through a closed suction system [125]. The hypothesis underlying this technique is that intraabdominal application of chemotherapy under pressure will enhance tumor drug uptake and aerosolizing and spraying chemotherapy will enhance the area of peritoneal surface covered by the drug.

Several experimental and clinical studies have been conducted to test the above-mentioned hypothesis [125-129]. Solass *et al*. performed PIPAC with cisplatin and doxorubicin in 3 end-staged patients with advanced PC of gastric, appendiceal and ovarian origin. They report that PIPAC required only 1/10 of the doxorubicin dose to achieve higher tumor concentrations as compared to HIPEC. High tissue concentrations of doxorubicin were reported. Moreover, fluorescence microscopy showed nuclear presence of doxorubicin throughout the whole peritoneal layer and up to deeply into the retroperitoneal fatty tissue. They concluded that PIPAC was well tolerated with excellent local exposure and low systemic exposure [127]. Moreover, PIPAC appeared to be associated with very limited hepatic and renal toxicity even after repeated PIPAC [130, 131]. On the other hand, Khosrawipour *et al*. reported that the depth of

doxorubicin penetration was significantly higher in tissues directly exposed to the aerosol jet when compared to the side wall, in an *ex vivo* PIPAC model [132]. In a phase II study conducted by Tempfer *et al.*, 64 patients with recurrent ovarian, fallopian or peritoneal cancer with PSM were treated with 3 courses doxorubicin and cisplatin based PIPAC. PIPAC was well tolerated, easy to perform and associated with a better quality of life as compared to systemic chemotherapy, with the absence of grade 4 toxicities [129]. Demtröder *et al.* performed a retrospective analysis including 17 patients with pretreated (surgery alone or combined with systemic chemotherapy) colorectal peritoneal metastases, who had received up to 6 cycles of oxaliplatin based PIPAC. Repeated PIPAC with oxaliplatin could induce regression of the peritoneal metastases, with low toxicities [133]. However, it should be taken into account that patients included in these trials are highly selected and often have had extensive surgery and were already heavily pretreated with several lines of systemic chemotherapy. The potential limited access of the aerosolized chemotherapy due to the presence of adhesions is not taken into account. Moreover, incomplete responses warrants further cytoreduction. However, it has been reported that PIPAC should not be combined with CRS due to the potential of increased local toxicity [134]. Recently, Kakchekeeva *et al.* introduced electrostatic PIPAC (ePIPAC), hypothesizing that electrostatic charging the aerosol particles may further enhance the pharmacologic properties of PIPAC [135]. They performed a comparative study of PIPAC and ePIPAC assessing the pharmacologic properties using an *in vivo* porcine model. They reported that ePIPAC has the potential to allow more efficient drug uptake, further dose reduction, a significant shortening of the time required for PIPAC application, further improving health and safety measures.

Today, there are no phase III trial data available for PIPAC emphasizing that

this is still an experimental treatment, which should be further investigated within the context of controlled clinical trials. These data will be important in identifying the role of PIPAC in the treatment of PSM patients. Today, PIPAC can play a role as a new palliative treatment option in highly selected patients with PSM.

Drug delivery systems

As was previously mentioned, the ideal drug for IP chemotherapy should have a high peritoneal tissue concentration and this should occur in conjunction with slow diffusion of the chemotherapy solution through the peritoneal membrane and deep in the subperitoneal space. However, today there are no drugs specifically designed for IP use. Therefore, over the past years, a lot of research has been focusing on the use of drug delivery systems to optimize IP drug delivery and to prolong the residence time of the drug in the peritoneal cavity with minimal systemic toxicity. These delivery systems include microspheres, nanoparticles, liposomes, micelles, injectable systems and implantable systems [101, 136]. In a preclinical study, De Smet *et al*. reported the development of a stable nanocrystalline paclitaxel formulation which was of interest for the treatment of ovarian PSM via HIPEC [137]. Xu *et al*. designed a thermosensitive injectable drug delivery hydrogel assembled by paclitaxel-incorporated nanoparticles with an improved bioavailability and induced effective antitumor efficacy in a colorectal PSM mouse model [138]. Thermosensitive hydrogels can transfer from free-flowing sol to a gel at physiological temperature and are interesting candidates for sustained drug delivery.

Conclusion

The combination of CRS and IP chemotherapy should now be considered standard of care for PSM from appendiceal epithelial cancers, colorectal cancer and

peritoneal mesothelioma. Although there is a near universal standardization regarding the CRS, there is still a much-needed standardization amongst the various IP chemotherapy treatment modalities used today in clinical practice. Although today, trends in the IP protocols, concerning the reduced dosing of oxaliplatin and the triple dosing regimen of mitomycin C are observed; pharmacologic evidence should be provided to answer important questions raised by the myriad of variables associated with IP chemotherapy. Furthermore, new and innovative IP chemotherapy concepts, like PIPAC, should be investigated in well-designed and adequately powered phase III clinical trials.

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Table 1: Overview of pharmacologic properties of the chemotherapy drugs most frequently selected for IP application.

Drug	Type	Molecular weight (Daltons)	Dose	Exposure time	AUC-ratio	Penetration depth	Thermal augmentation	Remarks
Cisplatin	Alkylator	300.1	50 mg/m^2 – 250 mg/m^2	30 minutes – 20 hours	7.8-21	1-5 mm	Yes	Dose limiting nephrotoxicity
Carboplatin	Alkylator	371.25	200 mg/m^2 – 800 mg/m^2	30 minutes – 20 hours	1.9-10	0.5-9 mm	Yes	
Oxaliplatin	Alkylator	397.3	200 mg/m^2 – 460 mg/m^2	30 minutes – 20 hours	3.5-16	1-2 mm	Yes	
Melphalan	Alkylator	305.2	50 mg/m^2 – 70 mg/m^2	90 minutes – 120 minutes	93		Yes	Rapid degradation
Mitomycin C	Antitumor antibiotic	334.3	15 mg/m^2 – 35	90 minutes – 150	10-23.5	2 mm	Yes	

			mg/ m²	minutes				
Doxorubicin	Antitumor antibiotic	579.99	15 mg/m² – 75 mg/m²	90 minutes	162 - 579	4-6 cell layers	Yes	
Docetaxel	Antimicrotubuli agent	861.9	45 mg/m² – 150 mg/m²	30 minutes – 23 hours	552	NA	Conflicting data	Cell-cycle specific
Paclitaxel	Antimicrotubuli agent	853.9	20 mg/m² – 180 mg total dose	30 minutes – 23 hours	1000	> 80 cell layers	Conflicting data	Cell-cycle specific
5-fluorouracil	Antimetabolite	130.08	650 mg/m² for 5 days (EPIC)	23 hours	250	0.2 mm	Yes (mild)	Cell-cycle specific
Gemcitabine	Antimetabolite	299.5	50 mg/m² – 100	60 minutes – 24	500	NA	NA	Cell-cycle specific

			0 mg/m^2	hours				
Pemetrexed	Antimetabolite	471.4	500 mg/m^2	24 hours	19.2	NA	NA	Cell-cycle specific

AUC: Area-under-the-curve; thermal augmentation: cytotoxicity of the chemotherapeutic agent is enhanced by hyperthermia

Table 2: Hyperthermic intraperitoneal chemotherapy (HIPEC)- and Bidirectional Intraoperative Chemotherapy (BIC)-regimens.

Cisplatin-based regimens
Sugarbaker Regimen
1. Add cisplatin to 2 L 1.5% dextrose peritoneal dialysis solution 2. Add doxorubicin to the same 2 L 1.5% peritoneal dialysis solution 3. Dose of cisplatin is 50 mg/m^2 and doxorubicin is 15 mg/m^2 for 90-minute HIPEC treatment *Intravenous Chemotherapy* 4. Add ifosfamide 1300 mg/m^2 to 1 L 0.9% sodium chloride. Begin continuous IV infusion over 90 minutes simultaneous with intraperitoneal chemotherapy 5. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 15 minutes prior to ifosfamide infusion 6. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 4 hours after ifosfamide infusion 7. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 8 hours after ifosfamide infusion
National Cancer Institute Milan Regimen
1. 15.25 mg/L of doxorubicin and 43 mg/L of cisplatin for 90-minute HIPEC treatment 2. Chemotherapy solution 4-6 liters based on capacity of the peritoneal space
Oxaliplatin-based regimens
Elias High Dose Oxaliplatin Regimen

1. Add oxaliplatin to 2 L/m2 5% dextrose solution
2. Dose of oxaliplatin is 460 mg/m2
3. 30-minute HIPEC treatment

Intravenous Component

4. Add 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs one hour before intraperitoneal chemotherapy

Glehen Medium Dose Oxaliplatin Regimen

1. Add oxaliplatin to 2 L/m^2 5% dextrose solution
2. Dose of oxaliplatin is 360 mg/m^2
3. 30-minute HIPEC treatment

Intravenous Component

4. Add 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs one hour before intraperitoneal chemotherapy

Wake Forest University Oxaliplatin Regimen

1. Add oxaliplatin to 3 L 5% dextrose solution
2. Dose of oxaliplatin is 200 mg/m^2
3. Two hour HIPEC treatment

Mitomycin C-based regimens

Sugarbaker Regimen

1. Add mitomycin C to 2 L 1.5% dextrose peritoneal dialysis solution
2. Add doxorubicin to the same 2 L 1.5% peritoneal dialysis solution
3. Dose of mitomycin C and doxorubicin is 15 mg/m^2 for each chemotherapy agent
4. Add 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs simultaneous with intraperitoneal chemotherapy

Dutch High Dose Mitomycin C Regimen: 'Triple Dosing Regimen'

1. Add mitomycin C to 3 L 1.5% dextrose peritoneal dialysis solution
2. Add mitomycin C to the 1.5% peritoneal dialysis solution at a dose of 17.5 mg/m^2 followed by 8.8 mg/m^2 at 30 minutes and 8.8 mg/m^2 at 60 minutes
3. Total dose of mitomycin C 35 mg/m^2 for 90-minute HIPEC treatment

American Society of Peritoneal Surface Malignancy Low Dose Mitomycin C Regimen: 'Concentration-Based Regimen'

1. Add mitomycin C to 3 L 1.5% dextrose peritoneal dialysis solution
2. Add mitomycin C to the 1.5% peritoneal dialysis solution at a dose of 30 mg/3 L followed by 10 mg at 60 minutes

3. Dose of mitomycin C 40 mg/3 L for 901-minute HIPEC treatment

Table 3: Early Postoperative Intraperitoneal Chemotherapy (EPIC)-regimens.

| **Early postoperative intraperitoneal chemotherapy with 5-fluorouracil on postoperative days 1 through 4 for adenocarcinoma from appendiceal, colonic, and gastric cancer** |
|---|
| 1. 5-Fluorouracil _____ mg (400 mg/m^2 for females and 600 mg/m^2 for males, maximum dose = 1400 mg) and 50 meq sodium bicarbonate in _____ mL 1.5% dextrose peritoneal dialysis solution via the Tenckhoff catheter daily for 4 days: start date _____, stop date _____ .
2. The intraperitoneal fluid volume is 1 L for patients ≤2.0 m^2 and 1.5 L for those >2.0 m^2.
3. Drain all fluid from the abdominal cavity prior to instillation, then clamp abdominal drains.
4. Run the chemotherapy solution into the abdominal cavity through the Tenckhoff catheter as rapidly as possible. Dwell for 23 hours and drain for 1 hour prior to next instillation.
5. Use gravity to maximize intraperitoneal distribution of the 5-fluorouracil. Instill the chemotherapy with the patient in a full right lateral position. After 30 minutes, direct the patient to turn to the full left lateral position. Change position right to left every 30 minutes. Continue turning for the first 6 hours after instillation of chemotherapy solution.
6. Monitor with pulse oximeter during the first 6 hours of intraperitoneal chemotherapy.
7. Continue to drain abdominal cavity after final dwell until Tenckhoff catheter is removed. |
| **Early postoperative intraperitoneal chemotherapy with paclitaxel on postoperative days 1-5 for peritoneal mesothelioma and ovarian cancer** |
| 1. Paclitaxel _____ mg (20 to 40 mg/m^2 x _____ m^2) (maximum dose = 80 mg) in 1000 mL 6% Hespan® (B. Braun, Irvine, CA) via Tenckhoff catheter daily: start date _____, stop date _____ .
2. Instill as rapidly as possible via Tenckhoff catheter. Dwell for 23 hours. Drain from Jackson-Pratt drains for one hour prior to next instillation.
3. During the initial 6 hours after chemotherapy infusion, the patient's bed should be kept flat. The patient should be on the right side during instillation. Turn at 30 minutes post instillation onto the left side and continue to change sides at 30-minute intervals for 6 hours.
4. Monitor with pulse oximeter during the first 6 hours of intraperitoneal chemotherapy.
5. Continue to drain abdominal cavity by Jackson-Pratt drains after the last dose of intraperitoneal chemotherapy. |
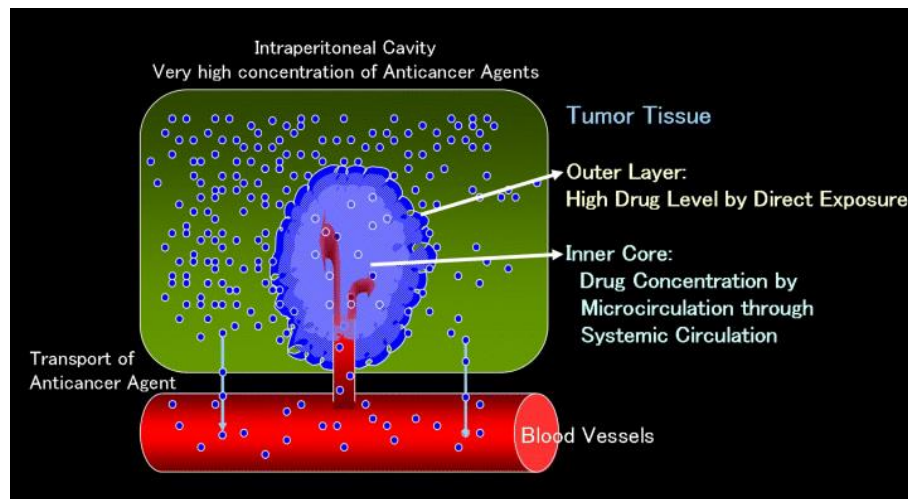
Figure 1: Pharmacologic concept of bidirectional intravenous and intraperitoneal chemotherapy. (Adapted from Fujiware K. Three ongoing intraperitoneal chemotherapy trials in ovarian cancer. Int J Gynecol Cancer. 2012; 17(1), 2, with permission.)(137)