Review

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Overview of the optimal perioperative intraperitoneal chemotherapy regimens used in current clinical practice

DOI 10.1515/pap-2017-0003
Received February 5, 2017; accepted March 20, 2017;
previously published online April 7, 2017

Abstract: 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 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 among 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: bidirectional intraoperative chemotherapy (BIC), early postoperative intraperitoneal chemotherapy (EPIC), hyperthermic intraperitoneal chemotherapy (HIPEC), peritoneal surface malignancy

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 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]. Eveno et al. provided a thorough overview of randomized controlled trials evaluating CRS and HIPEC vs. other strategies in prevention and therapy of PSM [11]. The combined treatment modality should now be considered standard of care for PSM from appendiceal epithelial cancers, colorectal cancer and peritoneal mesothelioma [12–14]. Promising results have also been published for HIPEC in ovarian cancer and gastric cancer [5, 9, 15]. Although there is now a clearly defined standardization of CRS, based on the work by Sugarbaker et al. [16, 17], no standardized intraperitoneal (IP) chemotherapy treatment modalities exist. Variables to be considered are normothermic vs. HIPEC, open vs. 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 [18] and EPIC [19]. There is a pressing need to generate pharmacologic data working toward standardization among the myriad of IP treatment protocols currently applied. The current IP chemotherapy regimens are non-standardized, poorly predictable and based largely on extrapolation of systemic chemotherapy data (Figure 1). In this manuscript, we review the current IP chemotherapy practice for colorectal, appendiceal, gastric, ovarian PSM and peritoneal mesothelioma.

Ideal IP chemotherapy regimens

The ideal IP chemotherapy regimen has to meet two important requirements: First, we have to construct the pharmacologic best way of delivery of our cancer chemotherapy agent from the moment of application until the penetration into the individual tumor cell. Pharmacology of IP chemotherapy can be artificially divided between pharmacokinetics and pharmacodynamics. Whereas pharmacokinetics

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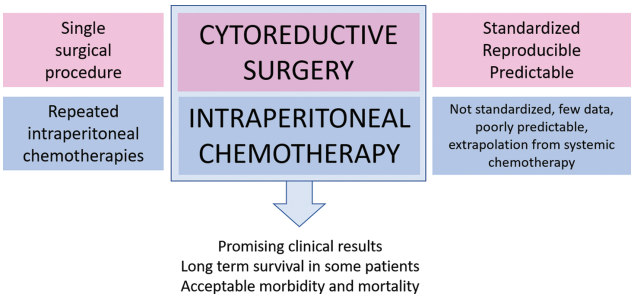

Figure 1: Treatment of peritoneal surface malignancy.

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 × time graph. The area-under-the-curve (AUC) ratio IP/IV is important in that it quantifies the dose intensity expected in the treatment of PSM. 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. Pharmacodynamics data are depicted in a concentrations × effect graph.

A second equally important requirement is the choice of the correct cancer chemotherapy drug with a cytotoxic activity against that specific cancer cell [19]. This emphasizes the increasing importance of chemosensitivity testing, toward 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, metabolization 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.

IP cancer chemotherapy regimens for colorectal or appendiceal PSM

Table 1 summarizes the most frequently used IP cancer chemotherapy regimens in colorectal and appendiceal PSM. The two dominant cancer drugs that form the backbone of these regimens are oxaliplatin and mitomycin C.

Oxaliplatin

Oxaliplatin (oxalato-1,2-diaminocyclohexane-platinum(II)) is a third-generation platinum complex with proven cytotoxicity in colon and appendiceal neoplasms [24]. In a dose escalation and pharmacokinetic study, Elias et al. demonstrated that 460 mg/m^2 of oxaliplatin in 2 L/m^2 of chemotherapy solution over 30 min was well tolerated [25, 26]. The low AUC ratio is compensated by the rapid absorption of the drug into the tissue, being the reason for the short application time. Since there initiation into the IP chemotherapy regimens at the beginning of the 2000s, we see a trend toward lower oxaliplatin-dosed

Table 1: Hyperthermic intraperitoneal chemotherapy (HIPEC)- and bidirectional intraoperative chemotherapy (BIC)-regimens.

Oxaliplatin-based regimens
Elias high dose oxaliplatin regimen
1. Add oxaliplatin to 2 L/m^2 5 % dextrose solution
2. Dose of oxaliplatin is 460 mg/m^2
3. 30-min 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 1 h 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-min 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 1 h 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 min and 8.8 mg/m^2 at 60 min
3. Total dose of mitomycin C 35 mg/m^2 for 90-min 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 min
3. Dose of mitomycin C 40 mg/3 L for 90-min HIPEC treatment

regimens. This is based on a growing concern for unacceptable bleeding complications with the initial 460 mg/m^2-based regimens. In a phase I trial, Elias et al. himself evaluated the pharmacokinetics of heated IP oxaliplatin administered in increasingly hypotonic solutions of 5 % dextrose [27]. 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 [28]. Chalret du Rieu et al. performed a population pharmacokinetics study, including 75 patients, treated with CRS and oxaliplatin-based HIPEC [29]. 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 [30]. 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 [31]. Unknown to most this degradation of oxaliplatin in normal saline only accounts for less than 10 % of the total amount at 30 min, as when applied during HIPEC. Moreover, oxaliplatin degradation was associated with the formation of its active drug form [Pt(dach)Cl_2] [32, 33]. Different oxaliplatin-based HIPEC regimens are used in current clinical practice: "Elias High Dose Oxaliplatin Regimen" [25], "Glehen Medium Dose Oxaliplatin Regimen" and the "Wake Forest University Oxaliplatin Regimen" [24].

Mitomycin C

Mitomycin C is an alkylating tumor antibiotic extracted from *Streptomyces* species which most important mechanism of action is through DNA cross-linking. Jacquet et al. reported a clear pharmacokinetic advantage after IP administration with an AUC IP/IV ratio of 23.5 [34]. It is used for PSM from colorectal cancer, appendiceal cancer, ovarian cancer, gastric cancer and, for diffuse malignant peritoneal mesothelioma both as HIPEC and as EPIC [2, 3, 34–38]. Barlogie et al. suggested *in vitro* thermal enhancement of mitomycin C [39, 40]. Our pharmacokinetic data in 145

HIPEC patients suggest that the largest proportion (62%) of the total drug administered remained in the body at 90 min [36]. 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" [36], The "Dutch High Dose Mitomcyin C Regimen: Triple Dosing Regimen" [41] and the "American Society of Peritoneal Surface Malignancy Low Dose Mitomycin C Regimen: Concentration-based Regimen" [42].

Body surface area-based or concentration-based 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/m^2) 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 [43]. The Dedrick formula on itself is an application of Fick's law of diffusion. Rubin et al. [44] however, demonstrated there is an imperfect correlation between actual peritoneal surface area and calculated BSA. 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 vs. closed abdomen). From the Dedrick formula we know that peritoneal concentration and not peritoneal dose is the driving diffusion force [43]. The importance of this has been discussed by Elias et al. [45] 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 [46]. 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 [47]. 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. Currently, there is an ongoing randomized trial at our hospital evaluating the pharmacology and morbidity of both dosing methods, entitled "concentration-based vs. body surface area-based perioperative intraperitoneal chemotherapy after optimal cytoreductive surgery in colorectal peritoneal carcinomatosis treatment: randomized non-blinded phase III clinicaltrial (COBOXtrial)" (https://clinicaltrials.gov/ct2/show/NCT03028155).

Clinical results

Table 2 summarizes the clinical trials comparing oxaliplatin-based and mitomycin c-based HIPEC [45–47]. Except for the study by Leung et al. all these studies show similar clinical outcome which seems to suggest non-inferiority of either drug [47]. All of these reports, however, have serious methodological issues (selection bias, historical bias, ...). A randomized control trial is at order to solve this issue. A multi-center, open-label, randomized phase II trial has been conducted to evaluate hematologic toxicities after HIPEC with oxaliplatin and mitomycin C in patients with appendiceal tumors (https://clinicaltrials.gov/ct2/show/NCT01580410). Time to progression after oxaliplatin- or mitomycin C-based HIPEC has also been evaluated. The accrual is completed and we are now awaiting the results.

IP cancer chemotherapy for PSM of gastric cancer, ovarian cancer, mesothelioma and sarcoma

The predominant IP regimens in this setting are cisplatin-based.

Table 2: Clinical studies of oxaliplatin-based vs. mitomycin-C-based HIPEC.

Year	Author	n	Type	Uni/multi	Result
2008	Elias	523	Retrospective	Multi [23]	MMC = Oxali
2014	Hompes	95	Retrospective	Bicentric	MMC = Oxali
2014	Prata-Villaverde	539	Retrospective	Multi (>15)	MMC = Oxali except PSDSS I/II (MMC 54.3 vs. 28.2 months)
2016	Leung	201	Retrospective	Unicentric	Oxali (OS 56 vs. 29 months)

Cisplatin

Cisplatin (cis-diamminedichloroplatinum-III, CDDP) is an alkylating agent that causes apoptotic cell death by formation of DNA adducts [48]. Both normothermic and hyperthermic IP applications have been explored in the treatment of ovarian cancer, gastric cancer and peritoneal mesothelioma [4, 18, 49–54]. It is eliminated by renal excretion and consequently the main concern with its use is renal toxicity [55]. Urano et al. showed an excellent *in vitro* and *in vivo* thermal augmentation of cisplatin [56]. Current applied cisplatin-based HIPEC regimens are the "Sugarbaker Regimen" [57] and the "National Cancer Institute Milan Regimen" [58] (Table 3).

Table 3: Cisplatin-based HIPEC 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-min HIPEC treatment
Intravenous chemotherapy
4. Add ifosfamide 1,300 mg/m^2 to 1 L 0.9 % sodium chloride. Begin continuous IV infusion over 90 min 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 min 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 h 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 h after ifosfamide infusion
National Cancer Institute Milan regimen
1. 15.25 mg/L of doxorubicin and 43 mg/L of cisplatin for 90-min HIPEC treatment
2. Chemotherapy solution 4–6 L based on capacity of the peritoneal space

Doxorubicin

Cisplatin-based regimens are often augmented with IP 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 [59–61]. 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 [18, 62–66]. More recently PEGylated liposomal doxorubicin has generated interest for HIPEC application due to its favorable pharmacokinetics [67, 68].

Bidirectional intraoperative chemotherapy (BIC)

Most current protocols advocate 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. 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 [69]. We also reported a clear pharmacokinetic advantage for the intraoperative IV administration of 5-fluorouracil [69]. A similar pharmacokinetic advantage and heat targeting of intraoperative IV ifosfamide was demonstrated [57]. 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. 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 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 [70–73]. 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. 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 4). This implies administrating multiple cycles, each with a dwell time of around 23 h 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 [74, 75]. 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 [19, 76–79]. 5-fluorouracil is not chemically compatible with other drugs in a mixed solution for infusion or instillation.

Taxanes

Paclitaxel and docetaxel, with their high molecular weight these molecules, have a remarkable high AUC ratio of respectively 853 and 861 [80]. The taxanes stabilize the microtubule against depolymerization, thereby disrupting normal microtubule dynamics [81]. There is evidence supporting additional mechanisms of action [82]. They exert cytotoxic activity against a broad range of tumors. This translates itself into a clear pharmacokinetic advantage for IP administration [83]. The data regarding possible thermal augmentation of taxanes are conflicting [82]. Taxanes have been used in a neoadjuvant intraperitoneal and systemic chemotherapy (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.

Neoadjuvant intraperitoneal and systemic chemotherapy

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

Table 4: 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 = 1,400 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 h and drain for 1 h 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 min, direct the patient to turn to the full left lateral position. Change position right to left every 30 min. Continue turning for the first 6 h after instillation of chemotherapy solution.
6. Monitor with pulse oximeter during the first 6 h 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 × _____ m^2) (maximum dose = 80 mg) in 1,000 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 h. Drain from Jackson-Pratt drains for 1 h prior to next instillation.
3. During the initial 6 h after chemotherapy infusion, the patient's bed should be kept flat. The patient should be on the right side during instillation. Turn at 30 min post instillation onto the left side and continue to change sides at 30-min intervals for 6 h.
4. Monitor with pulse oximeter during the first 6 h of intraperitoneal chemotherapy.
5. Continue to drain abdominal cavity by Jackson-Pratt drains after the last dose of intraperitoneal chemotherapy.

tumor biology and for reducing the extent of small PC nodules. Theoretically this approach, called NIPS, may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy [84]. Radiological and clinical responses with NIPS have been reported by several groups [84–87]. 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 [88]. Furthermore, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible. Table 5 lists the most commonly used NIPS regimens [83–88].

Table 5: Neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) – regimens.

Yonemura regimen (2016)

1. Oral S-1 is administered for 14 days at a dose of 60 mg/m^2/day, followed by 7 days rest prior to intraperitoneal chemotherapy administration
2. On day 1 docetaxel (30 mg/m^2) and cisplatin (30 mg/m^2) are administered by IP infusion
3. On day 8 (30 mg/m^2) and cisplatin (30 mg/m^2) are administered IV

Ishigami regimen

1. Oral S-140 mg/m^2 twice daily for 14 consecutive days followed by 7 days rest—I
2. Paclitaxel 50 mg/m^2 IV simultaneously with 20 mg/m^2 IP in 1 L normal saline over 1 h on day 1 and day 8
3. Regimen repeated every 3 weeks

Fujiwara regimen

1. Oral S-140 mg/m^2 twice daily for 14 consecutive days
2. Docetaxel 40–60 mg/m^2 IP in 1 L normal saline
3. Regimen repeated every 3 weeks

Sugarbaker regimen

1. Paclitaxel 20 mg/m^2 in 1 L 6 % Hespan (B. Braun, Irvine, CA, USA) via IP port or Tenckhoff catheter
2. Instill by gravity flow as rapidly as possible 5 days in a row
3. On day 3 of 5 day cycle, instill oxaliplatin 100–150 mg/m^2 IV in 250 mL D5W over 120 min. Start 30 min after IP paclitaxel

Conclusions

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 among the various IP chemotherapy treatment modalities used today in clinical practice. This manuscript reviewed the most commonly used IP regimens for HIPEC, EPIC and NIPS. Although today, trends in the IP protocols, such as the reduced dosing of oxaliplatin and the triple dosing regimen of mitomycin C are observed; more pharmacologic and clinical evidence should be generated to answer important questions raised by the myriad of variables associated with IP chemotherapy.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: Lemoine L is supported by the Agency for Innovation by Science and Technology (IWT) in Brussels, Belgium. Lemoine L is a researcher for the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk (LSM), Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital, Belgium.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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