



Application of IPC, HIPEC, and PIPAC

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13.1 Introduction

In the past, oncologists assumed peritoneal carcinomatosis (PC) was identical to distant metastases and, as such, regarded it as an incurable component of intra-abdominal malignancy only open to palliative treatment options. Since the 1980s, different treatment hypotheses for patients with isolated peritoneal metastases and primary peritoneal malignancies have emerged, based on the revised hypothesis that PC is a local-regional disease, which therefore warrants a local-regional therapeutic approach [64, 101, 103]. These new treatment protocols are based on a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC). In this setting, CRS aims at removing all macroscopic tumor, whereas the subsequent intraperitoneal (IP) chemotherapy seeks to elimi-

nate all residual microscopic tumor [81]. CRS and HIPEC have evolved over three decades and have demonstrated encouraging clinical results in several phase II and III trials [6, 41, 47, 76, 95, 102, 127–129, 133]. The combined treatment modality is now the standard of care for peritoneal metastases from appendiceal epithelial cancers, colorectal cancer, and peritoneal mesothelioma [24, 42, 115]. Promising results have also been published for HIPEC in recurrent ovarian cancer [5, 102]. Although there is now a near universal standardization regarding CRS, based on the work by Sugarbaker et al. [108, 117], no standardized IP chemotherapy treatment modalities exist. This chapter reviews the different treatment modalities for IP chemotherapy, with a special focus on the pharmacologic variables.

13.2 Pharmacology

Pharmacology of IP chemotherapy can be subdivided into pharmacokinetics and pharmacodynamics (Table 13.1). 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. The basic way of depicting pharmacokinetic data is by a concentration x

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Table 13.1 Pharmacokinetic and pharmacodynamic variables of intraperitoneal chemotherapy

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

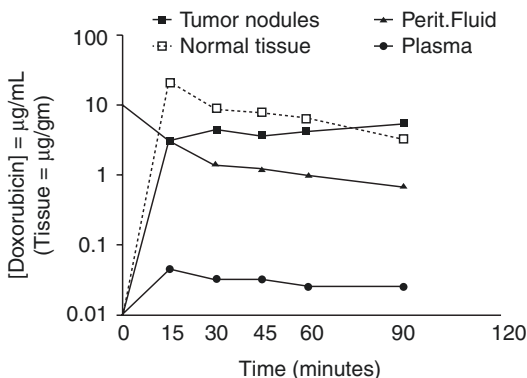


Fig. 13.1 Concentration-time graph of intraperitoneal doxorubicin during HIPEC. Doxorubicin concentration in plasma, peritoneal fluid, tumor nodules, and normal adjacent tissue. Data obtained from a single patient. (Adapted from [124])

time graph (Fig. 13.1). Pharmacodynamics subsequently looks into the effect of that cancer chemotherapy drug on the tumor. Pharmacodynamic data is depicted in a concentration x effect graph. Pharmacokinetic research seeks to deliver the chemotherapy in the most efficient way possible at the front door of the tumor.

13.3 Dose Intensification

The pharmacokinetic rationale of perioperative IP cancer chemotherapy is based on the dose intensification provided by the peritoneal-plasma barrier [13]. From 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 the same drug after IP administration. The peritoneal clearance is inversely proportional to the square root of its

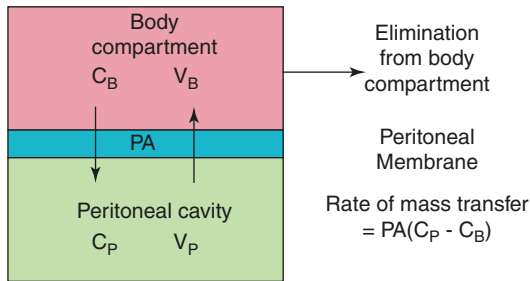


Fig. 13.2 The traditional two-compartment model of peritoneal transport; transfer of a drug from the peritoneal cavity to the blood occurs across the “peritoneal membrane.” The permeability area result (PA) governs this transfer. PA is calculated by measuring the rate of drug disappearance from the cavity, which is divided by the overall concentration difference between the peritoneal cavity and the blood (or plasma). 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 [14, 54]

molecular weight and results in a higher concentration in the peritoneal cavity than in the plasma after IP administration [16, 31]. This dose intensification over the peritoneal membrane is merely an application of Fick’s basic law of diffusion to transperitoneal transport. A simplified mathematical diffusion model considers the plasma to be a single compartment separated from another single compartment, the peritoneal cavity, by an effective membrane (Fig. 13.2).

This results in Eq. (13.1):

$$\text{Rate of mass transfer} = PA(C_{\text{Per}} - C_{\text{Bl}}) \quad (13.1)$$

where PA = permeability area (PA = effective peritoneal contact area $A \times$ permeability P), C_{Per} = concentration in peritoneal cavity, and C_{Bl} = concentration in the blood [33]. This simple conceptual model indicates the importance of the effective contact area [32]. Although the equation permits calculation of the pharmacokinetic advantage, the model does not reveal anything about the specific penetration of the cancer chemotherapy drug into the tissue or tumor nodule [34], nor does it predict the value of the effective contact area. The model simply describes the transfer between two compartments. After CRS, this concentration difference increases the pos-

sibility of exposing residual tumor cells to high doses of chemotherapeutic agents with reduced systemic concentrations and lower systemic toxicity. This advantage is expressed by the area under the curve (AUC) ratios of intraperitoneal (IP) versus plasma (IV) exposure. Already at this point, one should realize that the pharmacokinetic advantage does not automatically translate into better pharmacodynamics and thus effect.

13.4 Timing of Cancer Chemotherapy in Relation to Timing of Surgical Intervention

In the clinical application of intraperitoneal chemotherapy in PC patients, IP chemotherapy can occur at four points in relation to the time of surgery.

13.4.1 Neoadjuvant Bidirectional Chemotherapy

First, neoadjuvant bidirectional chemotherapy uses both the intraperitoneal and intravenous routes of chemotherapy administration prior to the CRS. It has been suggested as an option for reducing dissemination to the extra-abdominal space, for testing the tumor biology, and for reducing the extent of small PC nodules. Theoretically, this approach, which is called neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy [137]. Radiological and clinical responses with NIPS have been reported by several groups [113, 137, 138, 141]. 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 intraperitoneal 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 [25]. Furthermore, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible.

13.4.2 Hyperthermic Intraperitoneal Perioperative Chemotherapy (HIPEC)

Hyperthermic intraperitoneal perioperative chemotherapy is the most widely explored modality that has consistently clinically improved outcomes in many phase II and III trials [9, 19, 21, 35, 43, 51, 61, 127–129, 131, 132, 134].

13.4.3 Normothermic Intraperitoneal Preoperative Chemotherapy (NIPEC)

Over the past years, several experimental studies have been conducted to investigate what exactly is the added benefit of combining hyperthermia to the CRS alone [8, 45, 63, 80, 100, 140]. In vitro experiments performed by Michalakis et al. [80] indicate that short-term treatment of carcinoma cells with high concentrations of paclitaxel in both normothermic and hyperthermic settings is equally effective for cell growth arrest. Klaver et al. [63] used a rodent model of colorectal PC to demonstrate that the effectiveness of intraoperative intraperitoneal perfusion after CRS is not dependent on hyperthermia. Sørensen et al. [100] showed that NIPEC provided high intraperitoneal mitomycin C concentrations and increased bioavailability in extraperitoneal tissue, while hyperthermia at 41 °C did not modify the mitomycin C pharmacokinetics. On the other hand, Glehen et al. [45] evaluated the effect of hyperthermia on the pharmacokinetics and tissue distribution of intraperitoneal melphalan in a rodent model. They report that hyperthermia resulted in a decreased area under the curve (AUC) of melphalan in the peritoneal fluid, without increasing the plasma AUC, and increased intra-abdominal tissue concentrations.

Also, several clinical trials addressed the question regarding the additional effect of hyperthermia [105]. In a meta-analysis of the randomized controlled trials on adjuvant IP chemotherapy for resectable gastric cancer, Yan et al. [132] observed a trend toward survival improvement in patients receiving NIPEC. However, this was not significant with patients receiving early postoperative chemotherapy (EPIC) or delayed postoperative IP chemotherapy. A more recent meta-analysis comparing different methods of intraoperative and IP chemotherapy for patients with gastric cancer [53] showed that both HIPEC and NIPEC were associated with significant improvement in overall survival and that hyperthermia had no additional effect. In a retrospective analysis determining the risk factors of anastomotic leak after low colorectal resection, Averbach et al. [4] reported that anastomotic leakage was not compromised by NIPEC. Additional hyperthermia was associated with high leak rate when extensive colon resection was performed.

A randomized phase II clinical trial is currently ongoing at Ghent University Hospital. This trial compares normothermic versus hyperthermic IP perioperative chemotherapy after optimal CRS in patients diagnosed with PC from colorectal origin, including appendiceal mucinous neoplasms and the pseudomyxoma syndromes (<https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-000701-77>). Initial results from this trial indicate no difference in its morbidity or mortality between normothermic and hyperthermic oxaliplatin-based IP intraoperative chemotherapy [48].

13.4.4 Early Postoperative Intraoperative Chemotherapy (EPIC)

Early postoperative intraoperative chemotherapy 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 mini-

mize nonuniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits.

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 during CRS, and it can be applied with or without HIPEC [109]. The proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell cycle-specific drugs such as 5-fluorouracil and the taxanes [112, 126]. This implies administering multiple cycles, each with a dwell time of around 23 hours before renewal. This ensures that all the residual tumor cells are susceptible to the cell cycle-specific drug.

Disadvantages associated with EPIC are the increased risks of infection and postoperative complications. Vaillant et al. [122] performed a prospective multicenter phase III trial randomizing patients with stage III colon cancer to either resection with IV 5-fluorouracil during surgery and IP administration of 5-fluorouracil for 6 days thereafter or resection alone. They report that the addition of IP chemotherapy during a short period of time after resection did not significantly reduce the risk of morbidity. However, the results suggested that it should be associated with IV chemotherapy to reduce both local and distant recurrences. Lam et al. [69] compared the overall and the recurrence-free survival of patients treated with HIPEC with mitomycin C and EPIC with 5-fluorouracil versus patients treated with HIPEC alone using oxaliplatin and simultaneous IV infusion of 5-fluorouracil. They reported that survival did not differ between the two groups. However, patients that received the combination of HIPEC and EPIC experienced more grade III/IV complications. A randomized phase II trial is currently ongoing at the Memorial Sloan Kettering Cancer Center. This study compares the efficacy and toxicity of EPIC and HIPEC after optimal CRS in patients with neoplasms of the appendix, colon, or rectum with isolated PC (<https://clinicaltrials.gov/ct2/show/NCT01815359>).

13.4.5 Long-Term Combined Intraperitoneal and Systemic Chemotherapy

A number of randomized phase III trials demonstrate that intravenous plus intraperitoneal chemotherapy improves survival in patients with optimally debulked stage III ovarian cancer, compared to intravenous chemotherapy alone [1, 3, 38, 59, 77, 87, 135]. This approach may be used as a “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. However, failure analysis for CRS plus perioperative chemotherapy indicates recurrent cancer occurs most frequently within the abdominal and pelvic cavity [10]. Although systemic metastases occur, treatment failures rarely occur in the liver, the 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.

13.5 Intraperitoneal Perioperative Chemotherapy

13.5.1 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 capillary endothelium and deep into the subperitoneal space. Pharmacologic variables that should be taken into account are the route of administration—either intraperitoneal only or intraperitoneal combined with intravenous administration.

The use of naked drugs versus nanoparticles, and single drugs versus multiple drugs, should also be considered. Table 13.2 summarizes the pharmacologic properties of the chemotherapy drugs most frequently selected for IP application [110].

To select a chemotherapy drug, one must know the response expected with this drug in patients with metastatic disease. The AUC ratio is important in that it estimates the dose intensity expected in the treatment of peritoneal metastases as compared to the toxicity experienced as a result of the systemic effects of the drug. As depicted in Table 13.2, many of the drugs selected for IP administration have a respectable AUC ratio. The drugs with the most favorable AUC ratios are mitomycin C, doxorubicin, gemcitabine, and pegylated liposomal doxorubicin.

The drugs that are used in the operating room are acute-phase drugs that can exert their effects in the absence of cell proliferation [126]. Those drugs that are used for EPIC are selected because they require cell division for their optimal effects. Such drugs are 5-fluorouracil and paclitaxel [112, 126].

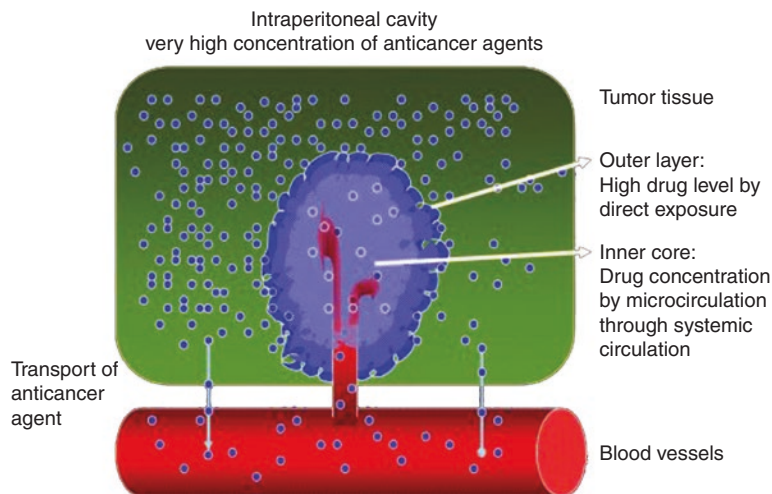
The retention of the IP chemotherapy drug is crucial in drug selection in that a response of the peritoneal metastasis is dependent upon the time over which a particular concentration of drug is present at the surface of the nodule. Slow clearance of the intraperitoneal drug and prolonged hyperthermia would be expected to cause a maximal response. The heat-augmented drugs that have a prolonged retention are gemcitabine, pegylated liposomal doxorubicin, and ifosfamide.

Another strategy for prolonged exposure of peritoneal nodules to chemotherapy requires the continuous infusion of the drug. By combining intraoperative IV and intraoperative IP cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer, which contains the tumor nodules, as depicted in Fig. 13.3. The best-studied intravenous chemotherapy agent targeted to peritoneal surfaces is ifosfamide. Continuous infusion of ifosfamide during HIPEC will result in cytotoxic levels of this drug within the peritoneal nodule over the 90 minutes

Table 13.2 Dosimetry and pharmacologic characteristics of cancer chemotherapy drugs used for intraperitoneal chemotherapy 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	360 mg/m ² -460 mg/m ²	30 minutes-20 hours	3,5-16	1-2 mm	Yes	Dextrose-based carrier
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 mg/m ²	90 minutes-150 minutes	10-23,5	2 mm	Yes	
Doxorubicin	Antitumor antibiotic	579,99	15 mg/m ² -75 mg/m ²	90 minutes	162-579	4-6 cell layers	Yes	
Docetaxel	Antimicrotubule agent	861,9	45 mg/m ² -150 mg/m ²	30 minutes-23 hours	552	NA	Conflicting data	Cell cycle specific
Paclitaxel	Antimicrotubule agent	853,9	20 mg/m ² -180 mg total dose	30 minutes-23 hours	1000	> 80 layers	Conflicting data	Cell cycle specific
5-Fluorouracil	Antimetabolite	130,08	650 mg/m ² for 5 days (EPIC)	23 hours	250	0,2 mm	Yes, mild	Cell cycle specific
Gemcitabine	Antimetabolite	299,5	50 mg/m ² -1000 mg/m ²	60 minutes-24 hours	500	NA	NA	Cell cycle specific
Pemetrexed	Antimetabolite	471,4	500 mg/m ²	24 hours	19,2	NA	NA	Cell cycle specific

Fig. 13.3 Pharmacological concept of bidirectional intravenous and intraperitoneal chemotherapy. (Adapted from Fujiwara K. et al. 2007, with permission)



of HIPEC [125]. Also, 5-fluorouracil has been used as a bolus infusion to augment the effect of hyperthermic intraperitoneal oxaliplatin [19].

A third mechanism for increased drug retention within the peritoneal space during HIPEC is repeated dosing of the chemotherapy agents. Verwaal et al. [128] used a triple dosing schedule for mitomycin C in order to increase the intraperitoneal exposure of this drug. They used half the drug dose at the initiation of HIPEC, one-quarter of it at 30 minutes, and another one-quarter of the dose at 60 minutes for a total of 90 minute HIPEC. By their calculation, this increased the effective dose of the mitomycin C.

In line with findings in systemic oncology, one can expect that the real question is not what the ideal drug is for IP chemotherapy, but rather what is the ideal drug for IP chemotherapy in this specific patient. The molecular heterogeneity within one tumor type of PC is staggering. These molecular subtypes have relevance for diagnosis, staging, prognosis, but increasingly so also for the choice of chemotherapeutic agent.

13.5.2 Dosage

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 (Table 13.2). These regimens take BSA as a measure for the effective peritoneal contact area: the peritoneal surface area in the Dedrick formula. However, Rubin et al. [91] demonstrate that there is an imperfect correlation between actual peritoneal surface area and calculated BSA, and there may 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—and thus 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 above, we know that peritoneal concentration and not peritoneal dose is the driving diffusion force. The importance of this has been discussed by Elias and Sideris [22]. In a clinical investigation where 2, 4, and 6 liters of perfusate solution was administered with a constant dose of chemotherapy, the more diluted intraperitoneal chemotherapy concentration retarded the clearance of chemotherapy and resulted in less systemic toxicity [111]. Therefore, it can be assumed that, with the diffusion model, less concentrated chemotherapy would penetrate less into the cancer nodules and into normal tissues. Concentration-based chemotherapy offers a more predictable exposure of the tumor nodules to the IP chemotherapy [78] and

thus more efficacy. Unfortunately, the price to be paid for a better prediction of the efficacy of the intraperitoneal chemotherapy is the high unpredictability of the plasmatic cancer chemotherapy levels and thus toxicity. Indeed, according to the abovementioned 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 [123]. These theoretical assumptions have since been validated; both in a preclinical PC rat model and in randomized clinical trial in humans [73, 74].

13.5.3 Carrier Solution

Hypotonic, isotonic, and hypertonic solutions with both low- and high-molecular-weight chemotherapy molecules have been explored. Salt-based, dextrose-based, hetastarch, or icodextrin solutions have been used [20, 67, 82–84, 86]. Moreover, the stability of the chemotherapeutic agent in the chosen carrier should also be considered. Mehta et al. [79] investigated the stability of oxaliplatin in both chloride-containing and chloride-deficient carrier solutions. They report that oxaliplatin concentration remained stable over a 2-hour period in a 5% dextrose-based solution. Increasing degradation rates of oxaliplatin were associated with increasing chloride concentrations, but this degradation was limited to a maximum of 10% after 30 minutes (the standard peritoneal perfusion time during HIPEC). Moreover, chloride seemed to promote the formation of the active cytotoxic drug form of oxaliplatin ($\text{Pt}(\text{dach})\text{Cl}_2$) and therefore could enhance its cytotoxic effect. The ideal carrier solution should enhance the exposure of the peritoneal surface and residual tumor cells to the chemotherapeutic agent. This is especially important in the setting of EPIC, where maintenance of a high dwell volume of perfusate over a prolonged time period improves the distribution of the drug and the effectiveness of the treatment. In a HIPEC setting with a relatively short dwell time, one could theoretically expect a pharmacodynamic advantage

of a hypotonic carrier through the mechanism of increased tissue and tumor absorption. Contrary to experimental studies supporting this hypothesis, Elias et al. [20] showed no increase in tumor penetration in humans. A concomitant high incidence (50%) of postoperative peritoneal bleeding and severe thrombocytopenia has contraindicated the further clinical use of hypotonic carriers.

13.5.4 Volume of Chemotherapy Solution

Since peritoneal metastases and free-floating tumor cells can be present anywhere on the peritoneal surface, the entire surface of the abdominal and pelvic cavity is the target. Substantial differences in the body composition of patients and differences in the actual HIPEC technique will result in a wide variety of perfusate volumes. In current practice, the volume of the perfusate is chosen quite arbitrarily. Based upon the above-stated equation concerning the mass transfer over the peritoneal-plasma membrane, increasing the solution-contact area A improves the mass transfer. Keshaviah et al. [57] demonstrated a linear rise in mass transfer in ten patients who were dialyzed with different volumes ranging from 0.5 up to 3 liters. Elias first published the importance of the volume of chemotherapy in determining systemic exposure to the drug [22]. Sugarbaker et al. [111] carried out a clinical investigation where 2 versus 4 versus 6 liters of chemotherapy solution were administered. The dose of chemotherapy solution in these studies was constant. They showed that a more diluted intraperitoneal chemotherapy concentration retarded the clearance of chemotherapy and led to a lesser systemic toxicity. It also must be assumed that the less concentrated chemotherapy would, according to the diffusion model, penetrate less into the cancer nodules and into normal tissues. These authors determined that it was necessary to regulate not only the chemotherapy dose but also the volume of chemotherapy solution to match the patient's BSA. A consistent drug dose and chemotherapy solution volume may be the optimal method to predict a maximal treatment in the abdomen with

a predictable bone marrow toxicity. Sugarbaker and colleagues suggested that variable volume is a dangerous practice with unpredictable systemic toxicities [111]. If the chemotherapy solution is administered until the abdomen is full, the contact area will increase. If the contact area is variable, the total absorption of drug cannot be predicted.

13.5.5 Temperature

Adding hyperthermia to IP chemotherapy will theoretically increase the tumor response by several mechanisms. First, heat alone has some direct antitumor effects. Although potentially important, the extent of the temperature elevation within the core of a tumor nodule is extremely limited. Selective cytotoxicity of malignant cells by heat is related to impaired DNA repair, increased protein denaturation, increased acidity, lysosomal activation, and increased apoptotic cell death [106].

A second and perhaps more important augmentation for hyperthermia is increased cytotoxicity with heat. Synergy between heat and cancer chemotherapy drugs is a complex pharmacological event. Augmented effects have been demonstrated for doxorubicin, cisplatin, mitomycin C, melphalan, oxaliplatin, and gemcitabine [116].

A third mechanism for increased cell kill of peritoneal metastases with hyperthermia is related to the increased depth of penetration of the cancer chemotherapy into tumor nodules. Jacquet et al. [55] reported increased tissue penetration of doxorubicin when the cancer chemotherapy solution was administered intraperitoneally at 43 °C. This increase in tissue concentration did not affect the pharmacokinetic advantages of the intraperitoneal administration. The elevated interstitial fluid pressure in tumor nodules compared to normal tissue is an acknowledged phenomenon [139]. A thermal dose-dependent decrease in interstitial fluid pressure in experimental solid tumors in an animal model has been reported by Leunig et al. [71].

However, the level of hyperthermia must be matched to the intraperitoneal cancer chemo-

therapy drug. With cisplatin, the higher the temperature, the greater the increase in cytotoxicity. In addition, those chemotherapy drugs that function as prodrugs may have a temperature threshold for maximal augmentation of cytotoxicity. Mitomycin C and gemcitabine are included in this category. It has been shown that gemcitabine, when heated to 43 °C, is impaired in its cytotoxicity. It is postulated that the conversion of gemcitabine triphosphate (the active agent) may be inhibited intracellularly at higher temperatures. Therefore, with this drug intraperitoneal heat should be limited to 41–42 °C [107]. The same situation is likely to exist with mitomycin C.

Urano et al. [121] identified the cancer chemotherapy drugs that are augmented by moderate hyperthermia of 41 °C. The drugs with the largest increase in cytotoxicity were cisplatin, melphalan, ifosfamide, and cyclophosphamide. These “super drugs” for hyperthermia are not all appropriate for intraperitoneal administration. Ifosfamide and cyclophosphamide are prodrugs which are expected to show little cytotoxicity when present with cancer cells in a chemotherapy solution. However, cisplatin and melphalan are said to enter the peritoneal metastases well, and the hyperthermia at 43–44 °C augments their expected therapeutic effect considerably.

As hyperthermia is the main logistical challenge hindering the widespread use of IP chemotherapy, the assumed increased cytotoxicity of adding hyperthermia to IP chemotherapy suggested by basic science needs urgent validation in clinical trials.

13.5.6 Pressure

Dedrick et al. [15] postulated that the penetration distance is equal to the square root of the ratio of the tissue diffusivity and the rate constant for drug removal from the tissue $(D/k)^{1/2}$. Using a rat model, Flessner et al. [30] showed a doubling of the extracellular space in the anterior abdominal wall of rats when the pressure of intra-abdominal peritoneal dialysis solution was raised from 0 to 4 cm H₂O. An increased effective diffusivity was postulated.

Animal experiments confirmed the increased intratumoral accumulation and antitumor effect of intraperitoneal doxorubicin and cisplatin when the intra-abdominal pressure was raised [23, 56]. Using a pig model, Facy et al. [27] report that high pressure (25 cm H₂O) enhances diffusion of oxaliplatin in the visceral and parietal peritoneum. The combination of high pressure and hyperthermia resulted in the highest tissue concentration of oxaliplatin. Increased intra-abdominal pressure is thought to generate a convective flux that forces the drug from the peritoneal cavity into the subperitoneal tissue. At the same time, intra-abdominal pressure may counteract the hydraulic capillary pressure and slow the outflow of the drug to the body compartment. Measurement of local cisplatin concentrations along the radii of peritoneal tumor nodules showed platinum penetration far beyond the 1 mm limit advocated by Los et al. [75]. The clinical limit of usable intra-abdominal pressure enhancement is dictated by respiratory and hemodynamic tolerance [93]. Clinical applications of HIPEC in intra-abdominal pressure settings have so far been limited to palliation of debilitating malignant ascites with laparoscopic HIPEC at 10–15 mm Hg [26, 40].

A novel approach involving pressurized intraperitoneal aerosol chemotherapy (PIPAC) takes advantage of the physical properties of pressure by using capnoperitoneum at a pressure of 12 mmHg to enhance drug uptake [120]. PIPAC is a laparoscopic method for repetitive delivery of low-dose intraperitoneal chemotherapy as a pressurized aerosol, claiming enhanced tumor penetration, homogeneous intraperitoneal drug distribution, and limited local and systemic toxicity. Due to these promising initial results, PIPAC is currently increasingly implemented in multiple centers worldwide.

13.5.7 Duration

A wide variation in the duration (ranging from 30 to 120 minutes) of IP chemotherapy protocols are reported (Table 13.2). The dose-response curves and their dependency on exposure time have been mathematically modeled by Gardner

[39]; according to this model, a plateau in tumor cell kill is reached, after which prolonged exposure time offers no further cytotoxic advantage. Theoretically, the most advantageous exposure time for cytotoxic effects in PC patients should be carefully weighed against systemic exposure and bone marrow toxicity and degradation processes. Duration of perioperative chemotherapy regimens should be pharmacology-driven and not arbitrary.

Of all variables, duration of IP chemotherapy is next to the choice of the drug the most important one. The best example for this is the combined negative randomized controlled trials (PRODIGE 7, COLOPEC, PROPHYLOCHIP) [46, 62, 88]. All three of them used a non-validated and flawed 30 minutes HIPEC with oxaliplatin. Already at the time of the study design, translational data were available demonstrating that oxaliplatin at 30 minutes was greatly inferior to oxaliplatin at 120 minutes [60]. Our group used apoptosis studies (activated caspase) to evaluate tumor cell death in PC nodules after CRS and HIPEC, once again both in a preclinical rat PC model and in human colorectal PC patients [73, 74]. In both instances the amount of apoptosis after 30 minutes of oxaliplatin-based HIPEC was very disappointing.

13.5.8 Irrigation Techniques

Although HIPEC has received the greatest attention in the search for eradication of the cellular component of peritoneal metastases following CRS, other mechanisms may be of value or less toxic. The mechanical removal of residual cancer cells through intraoperative irrigation prior to HIPEC may assist in the maximal eradication of cancer cells. Even after performing CRS for peritoneal metastases, large numbers of cancer cells will undoubtedly still be present within the ascites fluid: they will have been dislodged from the peritonectomy specimens or released from traumatized tumor nodules or the primary tumor [72]. In order to remove them, frequently throughout the CRS, dissection sites should be irrigated copiously and subsequently aspirated.

This frequent irrigation is to remove blood, tissue debris, and stray cancer cells as well as to clarify the anatomy for safe subsequent dissection. As a parietal peritonectomy procedure is completed, a large volume of warm saline irrigation should flood the peritonectomy site and the fluid should be vigorously manipulated to remove biologic fluids and cells. After the complete removal of the irrigation fluid, laparotomy pads or sterile towels should be placed in the peritonectomy site to prevent cancer cells from implanting within the raw surfaces as additional cytoreduction proceeds [94].

Upon completion of the cytoreduction but prior to HIPEC, an irrigation with a cytotoxic but non-chemotherapeutic agent should occur. Peroxide at 0.24% in 3 L of warm saline is used by Sugarbaker and colleagues [50]. Others have used 3 L of warm distilled water. Still others have utilized a diluted povidone-iodine solution [70]. Kuramoto et al. [66] have shown the value of mechanical cleansing of the peritoneal space with a large volume of fluid. They have used extensive intraperitoneal lavage (EIPL) to improve the survival of patients with gastric cancer and a high risk for implantation of gastric cancer cells. His strategy is to use 10 L of warm saline, 1 liter at a time in order to maximally irrigate away cancer cells that may be present.

13.6 Modes of Perfusion

Several different methodologies for administering HIPEC have been developed at centers experienced in the management of peritoneal surface malignancy.

13.6.1 Open Abdomen Technique

The open abdomen technique with a vapor barrier created by smoke evacuators has been used extensively at the MedStar Washington Hospital Center (Fig. 13.4) [108].

During the open coliseum technique (Fig. 13.5), the abdominal cavity is expanded after CRS by applying traction sutures on the

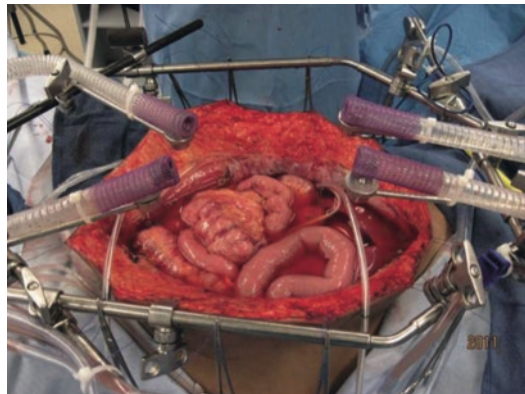


Fig. 13.4 The open abdomen technique to administer hyperthermic intraperitoneal perioperative chemotherapy (HIPEC). A vapor barrier is created by smoke evacuators [108]. (© 2017 with permission, Ciné-Med, Inc)

skin, which elevates the skin edge and provides the so-called coliseum [114]. This technique assures that the chemotherapy solution reaches all abdominal recesses. A heater circulator is used to maintain moderate hyperthermia (41–43 °C) within the abdomen and pelvis. Most treatment centers use a single inflow catheter that is moved in a clockwise direction from the right upper quadrant to beneath the left hemidiaphragm, to the left paracolic sulcus, to the pelvis, to the right paracolic sulcus, and then back to the right upper quadrant. Direct inflow within the small bowel regions is avoided. To remove the chemotherapy solution from the peritoneal space, one or more outflow catheters are placed in separate abdominal areas. The flow of the chemotherapy solution is usually set between 1 and 1.5 L/min. During the open abdomen technique, the abdomen is covered with a plastic sheet. A cruciate incision is made within the sheet to provide an access for manipulation of the abdominal viscera and to allow the heated chemotherapy solution to access all dependent parts of the abdomen and pelvis to ensure good drug distribution. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure.

The concern with the open abdomen technique is the potentially hazardous occupational exposure: i.e., exposing the operating room staff to the chemotherapy solution in liquid or vaporized form. Several studies have been per-



Fig. 13.5 During the open coliseum technique, the abdominal cavity is expanded after CRS by applying traction sutures on the skin, which elevates the skin edge and provides the so-called coliseum. The abdomen is covered with a plastic sheet. A cruciate incision is made within the sheet to provide an access for manipulation of the abdomi-

nal viscera and to allow the heated chemotherapy solution to access all dependent parts of the abdomen and pelvis in order to ensure good drug distribution. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure

formed to address this issue by measuring platinum levels in the blood and urine of healthcare workers and environmental (air and surfaces) samples during HIPEC [65, 92, 130]. They report that there is no risk of platinum exposure during the open coliseum technique when safety considerations are followed. Capron et al. [12] reported that double gloving can be used safely during HIPEC, as there was no detectable permeation of chemotherapy drugs during tests performed at 43 °C. These studies emphasize the need for a standardized protocol concerning HIPEC procedures with specific recommendations regarding environmental contamination risk management, personal protective equipment, and occupational health supervision [29].

13.6.2 Closed Abdomen Technique

Some groups close the abdomen prior to the HIPEC administration and then, following HIPEC, open the abdomen to perform anastomoses and to repair seromuscular tears, thereafter closing the abdominal incision. In this closed technique, the skin is only closed in a watertight fashion so that all of the structures of the ante-

rior abdominal wall are thoroughly treated by the chemotherapy solution. Some use a totally closed technique. In this methodology, the CRS is performed, and the abdomen is irrigated prior to the performance of intestinal anastomoses and the closure of the abdominal incision. Tubes and drains are positioned prior to the definitive closure of the abdomen. After closure of the abdomen, the perfusion of the heated chemotherapy solution is started [44, 68].

Advantages associated with the closed abdomen technique are the ability to rapidly achieve and to maintain hyperthermia in addition to the increased safety for operating staff. Another advantage believed to be associated with the closed HIPEC technique is that increased intra-abdominal pressure may increase the chemotherapy penetration into tissue. However, Ortega-Deballon et al. [85] report, in an experimental study, that the open technique had higher systemic absorption and abdominal tissue penetration of oxaliplatin than the closed technique. Facy et al. [28] used a pig model to demonstrate that tissue concentration of oxaliplatin was higher in the open technique even when high pressure was used in the closed abdomen technique. They conclude that the use of high pressure during the

closed abdomen technique does not outweigh the drawbacks. These drawbacks include the risk of recurrence along the abdominal incision and suture lines and lack of uniform distribution of the heated solution [18, 104]. Preferential flow circuits exist and some peritoneal surfaces are underexposed, which increases the risk of recurrence in these undertreated recesses. An attempt to better distribute the chemotherapy can be made by manually agitating the abdominal wall during the perfusion.

In a clinical study including patients diagnosed with PC of different origins, Halkia et al. [49] evaluated the differences in intraoperative parameters in patients receiving either the closed or open HIPEC technique. They concluded that both methods are safe and efficient in the treatment of PC with equal morbidity and mortality. They recommend the closed technique as the method of choice for frail patients due to more stable hemodynamic parameters.

13.6.3 Semi-open/Semi-closed Abdomen Techniques

The peritoneal cavity expander (PCE) was first described by Fujimura et al. [37]. During this technique, an acrylic cylinder is secured over the wound. This cylinder contains inflow and outflow catheters, is large enough to allow the small intestine to float in the heated perfusate, and allows manual manipulation of the perfusate. When compared with the closed perfusion technique, a more uniform drug distribution is achieved by temporarily increasing the volume of the peritoneal cavity. This method was mostly used for the treatment of gastric PC [52, 136].

The abdominal cavity expander, also referred to as the Landager technique, is a semi-closed abdomen technique with open abdomen, which ensures protection against potential hazardous occupational exposure and allows permanent access to the whole abdomen cavity, ensuring uniform drug distribution [7]. During this method, the skin edges are stapled watertight to a soft “abdominal cavity expander” supported by a Thompson self-retaining retractor positioned

over the abdomen. In this way, the level of the liquid can be widely raised above the level of the skin edges. The anterior abdominal wall and the wall edges are constantly exposed to the liquid [89]. The abdominal cavity expander has been recently used by Frøysnes et al. [36] in the treatment of colorectal PC.

13.7 Novel Approaches: PIPAC

PIPAC (Fig. 13.6) is a novel approach to deliver IP chemotherapy to patients diagnosed with PC [120]. During PIPAC, a normothermic capnoperitoneum (at a 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 [97, 98]. The hypothesis underlying this technique is that intra-abdominal application of chemotherapy under pressure will enhance tumor drug uptake and that 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 abovementioned hypothesis [96–99, 119]. Solass et al. [98] used a pig model to evaluate the stain distribution and direct penetration into the peritoneum during nebulization of methylene blue. They report that the stained peritoneal surface was larger and that the direct penetration of the stain into the peritoneum was enhanced after aerosol application when compared to conventional peritoneal lavage. They also performed PIPAC with cisplatin and doxorubicin in three end-stage 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. Doxorubicin was not only detected in tumor nodules, but nuclear staining was also demonstrated throughout the peritoneum, penetrating deeply into the retroperitoneal fatty tissue. They concluded that PIPAC was well tolerated with excellent local exposure and low

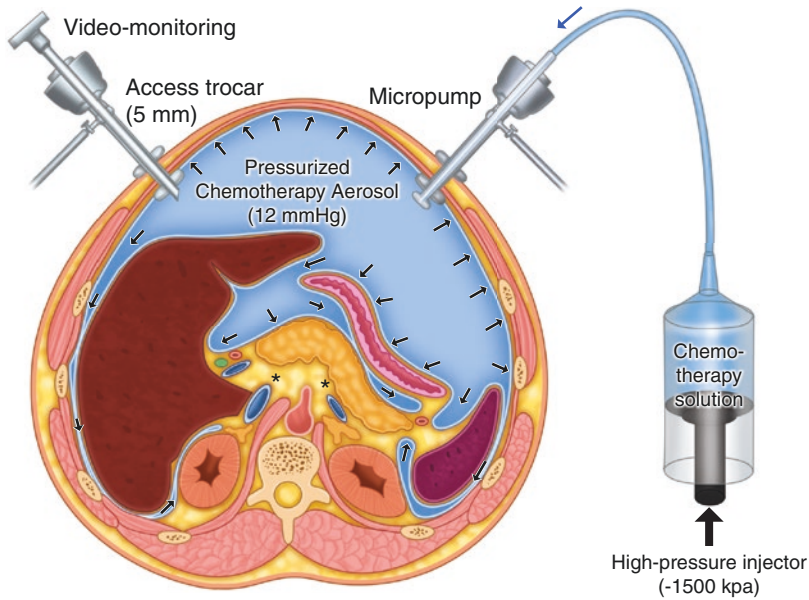


Fig. 13.6 During pressurized intraperitoneal aerosol chemotherapy (PIPAC), a normothermic capnoperitoneum (pressure of 12 mmHg) is established through a laparoscopic access in an operating room equipped with a

laminar airflow. A cytotoxic solution is nebulized into the abdominal cavity during 30 minutes and thereafter removed through a closed suction system. (Adapted from [99])

systemic exposure [99]. Khosrawipour et al. [58] in 2019 also reported increased tissue penetration with doxorubicin-based PIPAC. Moreover, PIPAC appeared to be associated with very limited hepatic and renal toxicity even after repeated PIPAC [11, 90]. In a phase II study conducted by Tempfer et al. [119], 64 patients with recurrent ovarian, fallopian, or peritoneal cancer with PC were treated with three courses doxorubicin- and cisplatin-based PIPAC. PIPAC was well tolerated, easy to perform, and associated with an increased quality of life as compared to systemic chemotherapy, with the absence of grade IV toxicities. Demtröder et al. [17] performed a retrospective analysis including 17 patients with pretreated (surgery alone or combined with systemic chemotherapy) colorectal peritoneal metastases, who had received up to six cycles of oxaliplatin-based PIPAC. Repeated PIPAC with oxaliplatin induced regression of the peritoneal metastases, with low toxicities. 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 considered. Moreover, incomplete responses warrant further cytoreduction. However, it has been reported that PIPAC should not be combined with CRS due to the potential of increased local toxicity [118].

Delivering chemotherapy as an aerosol might cause an increased risk of exposure to healthcare workers. The potentially hazardous occupational exposure when using PIPAC with cisplatin has been tested. The results indicated that PIPAC is in compliance with the labor safety laws and regulations of the European Community [96]. Further investigations are however needed to test the occupational safety and logistics when PIPAC is used with other cytostatic drugs.

Currently, there are two ongoing trials assessing PIPAC in women with gynecologic and gastric malignancies. The first ongoing trial is entitled: “A phase I, single-arm (non-randomized), open-label, dose escalation study with cisplatin and doxorubicin applied as pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with recurrent ovarian cancer and peritoneal

carcinomatosis (PIPAC-OV2)” (EudraCT-Nr. 2014-001034-28). In this trial, safety and tolerability of doxorubicin- and cisplatin-based PIPAC in a dose escalation scheme will be investigated until dose-limiting toxicity is reached. Moreover, pharmacologic studies will be included regarding hematological, liver, and renal function as well as the determination of cisplatin and doxorubicin plasma levels. The second ongoing trial is entitled “Feasibility, efficacy and safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent gastric cancer: an open-label, single-arm phase II clinical trial (PIPAC-GA1)” (<https://clinicaltrials.gov/ct2/show/NCT01854255>). In this trial, patients with recurrent gastric cancer will be treated with three cycles of doxorubicin- and cisplatin-based PIPAC. The primary outcome measure will be the clinical benefit rate according to the Response Evaluation Criteria in Solid Tumors (RECIST) after three cycles of PIPAC. Efficacy of this treatment will further be assessed by CT, tumor marker studies, survival, and safety.

In 2019, Alyami et al. [2] performed a systematic review of available data. They reported PIPAC to be feasible and safe. Data on objective response and quality of life were encouraging. Therefore, they propose PIPAC to be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. However, it needs to be validated by prospective studies.

Today, there is no phase III trial data available for PIPAC, emphasizing that this is still an experimental treatment that should be further investigated within the context of controlled clinical trials. This data will be important in identifying the role of PIPAC in the treatment of peritoneal surface malignancy patients. Today, PIPAC can play a role as a new palliative treatment option in highly selected patients with PC. Therefore, PIPAC cannot be directly compared with CRS and HIPEC, since the patient population and the intention to treat are different: palliative versus curative. Other potential roles of PIPAC should be explored—for example, in the neoadjuvant setting, to test tumor biology.

13.8 Conclusion

The combination of CRS and IP chemotherapy is now the standard of care for peritoneal metastases from appendiceal epithelial cancers, colorectal cancer, and peritoneal mesothelioma. Although there is a near universal standardization regarding CRS, there is still a much-needed standardization among the various IP chemotherapy treatment modalities used today in clinical practice. Pharmacologic evidence should be provided to answer important questions raised by the myriad of variables associated with IP chemotherapy. Tumor nodule apoptosis emerges as a valid pharmacologic endpoint in IP chemotherapy basic science. 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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