CHAPTER

10

Optimizing intraperitoneal drug delivery: pressurized intraperitoneal aerosol chemotherapy (PIPAC)

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1. Introduction

Every 30 s worldwide, a new patient is diagnosed with peritoneal metastasis, the spreading of cancer cells of gastrointestinal or gynecological origin into the peritoneal cavity [1]. Upon diagnosis of peritoneal metastasis, current therapy guidelines in Europe [2], the United States [3], and Asia [4] recommend palliative systemic chemotherapy for best supportive care. In spite of recent progress in targeted therapy, immunotherapy, cytoreductive surgery, and intraperitoneal chemotherapy, peritoneal metastasis remains a fatal disease and long-term survival is exceptional. Most physicians perceive peritoneal metastasis as a terminal disease and adopt a nihilistic attitude, considering symptom control as the best choice [5]. However, upon diagnosis of peritoneal metastasis, most patients want to live and live well [6]. Thus peritoneal metastasis is an unmet medical need that calls for the development of therapies able to prolong and preserve the quality of life.

The poor prognosis of patients with peritoneal metastasis might be explained by multiple factors, including poor tolerance to chemotherapy, steeper patient performance decline, intestinal dysfunction associated with tumor bowel invasion, undertreatment, and, last but not least, chemoresistance to cytotoxic drugs [7]. For example, patients with peritoneal metastasis have a significantly shorter survival rate than patients with metastasis in other locations such as the liver [7]. Why is peritoneal metastasis relatively resistant to chemotherapeutic drugs administered intravenously?

Most research into the resistance of peritoneal metastasis to chemotherapy has concentrated on molecular mechanisms of resistance and the hope was that development of better, targeted drugs would overcome this resistance and improve prognosis. However, in peritoneal metastasis, progress remained well below expectations: for example, in peritoneal metastasis of colorectal origin, the incremental advantage provided by targeted drugs remained lower than the advantage observed in other metastatic locations [7].

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Thus one must hypothesize that, beyond molecular mechanisms, other factors must play a role in the chemoresistance of peritoneal metastasis [8]. One possibility would be that anticancer drugs do not penetrate tissue efficiently (reviewed in Ref. [9]). Cytostatic drugs must indeed reach all the cancer cells in sufficient concentration to exert a therapeutic effect. If cytostatic drugs are unable to access all malignant clonogenic cells and/or tumor stem cells, no sustainable effect can be expected and peritoneal metastasis will progress under therapy. Logically, the rate of recurrence would then be expected to be largely independent of the mode of action of these drugs. This was confirmed in colorectal [7] and gastric [10] cancer; this resistance of peritoneal metastasis to therapy is observed in various primaries, different histologies, and heterogeneous tumor profiles. Another example of peritoneal disease resistant to systemic chemotherapy is pseudomyxoma peritonei (PMP). PMP is a borderline malignant condition where the peritoneal cavity is filled with several liters of mucoid jelly, leading to progressive respiratory and digestive failure and ultimately to death (reviewed in Ref. [11]). Probably due to the poor uptake of drugs into the mucoid mass, PMP is showing little response to any kind of systemic therapy [12].

Over the last 20 years, two factors have been identified that explain the relative chemoresistance of peritoneal metastasis: a limited vascular supply of the peritoneum and an increased intratumoral interstitial fluid pressure.

1.1 Poor vascularization of the peritoneum

Only 2%–5% of the cardiac minute volume vascularizes the peritoneum. Thus in patients with metastasis limited to the peritoneal cavity, most chemotherapy (95%–98%) will bypass the peritoneum, causing systemic toxicity with insufficient locoregional therapeutic effect. Moreover, the peritoneal microcirculation is characterized by a low capillary density in comparison to other organs [13]. For example, vascular density between peritoneal and sublingual microcirculation differs by a factor of two [14]. Both added factors result in poor peritoneal tissue uptake of compounds administered into the systemic blood compartment. For example, in a rodent model, distribution of luminescent mRNA complexes in the small bowel after intravenous injection was zero [15].

1.2 Increased interstitial intratumoral fluid pressure

Elevated interstitial fluid pressure is an obstacle to cancer treatment [16]. Many drugs used for systemic treatment of patients with cancer—high-molecular-weight compounds in particular—are transported from the circulatory system through the interstitial space by convection, that is, they are carried by streaming of a flowing fluid [17]. Thus increased interstitial fluid pressure leads to decreased fluid flow into the tumor node and therefore less uptake of drugs into the tumor. Cancer cells are therefore exposed to a lower effective concentration of therapeutic agent than normal cells, lowering the therapeutic efficiency. Several studies indicate that high interstitial fluid pressure in the tumor is correlated with poor prognosis [18].

2. Optimizing drug therapy in peritoneal metastasis

During the last three decades, many efforts have been devoted to optimizing drug therapy of peritoneal metastasis by delivering the drug directly into the abdominal cavity (reviewed in Ref. [19]). Local delivery has the potential for increased exposure of the peritoneal nodes to chemotherapeutic drugs and limits systemic toxicity. In peritoneal metastasis, there is established pharmacokinetic and tumor biology-related evidence that intraperitoneal drug administration is advantageous [20]. The

intraperitoneal-to-plasma drug area under concentration (AUC) ratio of drugs varies from a factor 10 to a factor 1000, depending on their molecular weight and hepatic and renal clearance [20]. Thus in theory and assuming the relative resistance of peritoneal metastasis to both conventional chemotherapeutic and targeted agents is explained by an insufficient drug concentration in the target tissue, intraperitoneal delivery should show superior efficacy.

Clinical data confirm the beneficial effect of intraperitoneal chemotherapy on peritoneal metastasis. For example, in ovarian cancer, several randomized clinical trials document an overall survival advantage for women with small volume residual advanced ovarian cancer who were treated with cisplatin-based intraperitoneal chemotherapy [21–24]. In ovarian cancer, the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to cytoreductive surgery also demonstrated significant survival benefit [25]. In peritoneal metastasis of gastric origin, repeated intraperitoneal chemotherapy using taxanes has been shown to be effective in several phase II trials and a phase III trial, with median survival times of 14.4–24.6 months and 1-year overall survival rates of 67%–91%. These results may lead to the approval of intraperitoneal taxanes, especially paclitaxel, for official insurance coverage in the near future [26]. Thus intraperitoneal drug delivery is an important adjunct to surgery and systemic chemotherapy in selected patients with cancer disease limited to the peritoneal cavity.

3. Limitations of intraperitoneal chemotherapy

However, intraperitoneal chemotherapy has several limitations, which are summarized in Table 10.1.

These concerns explain why, despite the positive effect of intraperitoneal chemotherapy on progression-free and overall survival in selected patients with small volume peritoneal cancer, only a few clinicians employ intraperitoneal chemotherapy other than in the trial setting [28]. The interest of pharmaceutical companies to extend the use of their proprietary drugs to intraperitoneal delivery is limited. In contrast to dermatology, no drug delivery systems and no specific formulations have been developed that address specifically the challenges raised by specific anatomical, physiological, and biochemical characteristics of the peritoneal barrier. To our knowledge, no drug is currently approved by the US Food and Drug Administration for intraperitoneal delivery. The problem of peritoneal metastasis is largely ignored by the pharmaceutical industry and patients with peritoneal metastasis continue to die in the absence of adequate, dedicated therapies.

TABLE 10.1 Limitations of intraperitoneal chemotherapy.

Adequacy of drug distribution throughout the entire peritoneal cavity
Limited depth of penetration of drugs into tumor tissue
Lack of dedicated formulations
Clearance of drug by retroperitoneal capillary flow
Unique toxic effects associated with local delivery
Catheter-linked complications
Added time, inconvenience, and cost

Adapted from Flessner MF. Pharmacokinetic problems in peritoneal drug administration: an update after 20 years. Pleura Peritoneum 2016;1:183–191.

4. Understanding drug uptake into peritoneal nodes

To address meaningfully the limitations of intraperitoneal chemotherapy, it is necessary to understand the pharmacological aspects of drug uptake into peritoneal metastasis. The so-called "peritoneal–plasma barrier" is responsible for the pharmacokinetic advantage of intraperitoneal drug delivery. Anatomically, this barrier consists of glycocalyx, peritoneal mesothelium, subserosal interstitium, and capillary walls, including the basal membrane. Functionally, the basal membrane of the capillaries is the most important in impeding the transfer of large molecules.

Drug uptake into peritoneal nodes is a complex process determined by several physical, chemical, and pharmacological laws and influenced by multiple factors. These multiple factors relate not only to the nature of the cytotoxic agent but also to the tumor tissue properties and environmental factors (Table 10.2).

It is evident that the nature of the target tissue to be treated determines drug uptake. Intuitively, drug uptake is expected to be more effective in loose tissue than in hard, fibrotic tissue. During tumor progression and under chemotherapy the extracellular matrix undergoes so-called epithelial–mesenchymal transition (EMT) [30], which is characterized by a progressive replacement of normal epithelial tissue by fibroblasts, a major cellular component of scar tissue [31]. During EMT, peritoneal mesothelial cells lose their epithelial-like characteristics, including dissolution of cell–cell junctions, tight junctions, adherence junctions and desmosomes, and loss of apical–basolateral polarity, and acquire a mesenchymal phenotype, characterized by actin reorganization and stress fiber formation, migration, and invasion [32]. These dramatic changes in tissue architecture reduce drug uptake into peritoneal metastasis, as compared to the normal peritoneum.

5. Pharmacokinetics aspects of intraperitoneal chemotherapy

The major benefit of intraperitoneal chemotherapy is the gain obtained in regional dose intensity [19]. Under normal conditions, when the drug is administered into the peritoneal cavity, high intraperitoneal concentrations can be

TABLE 10.2 Parameters involved in tissue drug uptake during intraperitoneal chemotherapy.

Tissue-related factors	Drug-related factors	Environmental factors
Permeability	Dose	Intraabdominal pressure
Vascularity/neoangiogenesis	Concentration	Carrier fluid
Interstitial fluid pressure	Molecular weight	Volume of carrier fluid
Cell density	Intrinsic ionic charge	Temperature
Extracellular matrix composition	Membrane binding	Presence of ascites
Healthy versus diseased state	Solubility (hydrophilicity vs. hydrophobicity)	Duration of exposition
	Diffusivity	Electrostatic loading
	Micronization	
	Formulation	

Adapted from Steuperaert M, Debbaut C, Segers P, Ceelen W. Modelling drug transport during intraperitoneal chemotherapy. Pleura Peritoneum 2017;2: 73–83.

reached, whereas systemic drug concentrations remain low. The difference in concentrations in these compartments is mainly caused by the slow absorption of the drugs from the peritoneal cavity into the systemic blood circulation (so-called peritoneal clearance). This is opposite to intravenous drug delivery for treating peritoneal disease, where systemic peak concentration is high and intraperitoneal concentration is low.

Low-molecular-weight compounds, such as glucose, electrolytes, or oxygen, are mainly transported through the peritoneum by diffusion; that is, they move from an area of high concentration to an area of low concentration. As we have seen, many drugs used for the treatment of patients with cancer—high-molecular-weight compounds in particular—are transported from the peritoneal cavity into the tumoral interstitial space by convection; that is, they are carried by streaming of a flowing fluid (reviewed in Ref. [29]). It has to be noted that uptake of a drug into peritoneal metastasis occurs not only from the intraperitoneal space, but also from the subserosal interstitium. However, the subperitoneal interstitium can also bind certain cytostatic agents, reducing drug penetration into peritoneal metastasis (reviewed in Ref. [9]).

Factors such as vascular endothelial growth factor (VEGF)-mediated increased permeability of the endothelial barrier to plasma proteins and alteration of the extracellular matrix in peritoneal metastasis modify the pharmacokinetics of intraperitoneal chemotherapy (reviewed in Ref. [13]). Neovascularization not only increases capillary permeability but also increases the surface of the capillary filter, thus facilitating protein extravasation and modifying oncotic pressure. Since VEGF acts on most of the factors intervening in Starling's equation, its expression results in an increase in fluid outflow and accumulation thereof within the peritoneal cavity, leading to the development of ascites [33]. This inversion of the fluid equilibrium counteracts drug uptake by convection into peritoneal nodes.

6. Pharmacodynamic aspects in intraperitoneal chemotherapy

High intraperitoneal drug concentration and optimal tissue exposure to the therapeutic agent are preconditions for effective intraperitoneal chemotherapy. However, the key factors for therapy success are not a sufficient drug concentration in the peritoneal fluid itself but rather adequate drug tissue penetration and achieving cytotoxic concentration of the drug within the peritoneal metastasis [34]. Unfortunately, when drugs are administered as liquid solutions into the peritoneal cavity, their penetration depth into peritoneal metastasis is very limited (Table 10.3).

This (very) limited drug penetration into the peritoneal nodes represents a major challenge in clinical practice. Depth of drug penetration into and beyond the peritoneum is determined by factors such as integrity of the glycocalyx, presence of intercellular junctions, collagen content in the extracellular matrix, neovessel density, and interstitial fluid pressure. Interstitial fluid pressure is increased in most solid tumors (reviewed in Ref. [16]). For example, interstitial fluid pressure values as high as 33 mmHg have been recorded in some sarcomatous tumors [35]. Our own measurements of interstitial fluid pressure in diseased human peritoneal nodules showed intratumoral fluid pressure up to 20 cmH_2O, depending on the size and degree of tumor regression (data on file). Increased interstitial fluid pressure leads to a decreased uptake of drugs or therapeutic antibodies into the tumor.

A further problem is the incomplete exposure of the peritoneum to liquid intraperitoneal chemotherapy. Experimental data obtained in the animal model suggest limited exposure of the peritoneal surface during conventional peritoneal lavage. When peritoneal dialysis was carried out in rodents with a solution containing methylene blue and bovine serum albumin,

TABLE 10.3 Main characteristics of drugs commonly administered in intraperitoneal chemotherapy.

Drug	Molecular weight	AUC ratio	Thermal enhancement	Penetration depth
Alkylating agents				
Mitomycin C	334.3	13–80	+	2–5 mm
Melphalan	305.2	17–63	+	NA
Platinum compounds				
Cisplatin	300.1	12–22	+	1–5 mm
Carboplatin	371.3	15–20	+	0.5 mm
Oxaliplatin	397.3	16	+	1–2 mm
Topoisomerase inhibitors				
Irinotecan	677.2	15[a]	±[b]	NA
Doxorubicin	580.0	162–230	+	4–6 cell layers
Antimicrotubule agents				
Paclitaxel	853.9	550–2300	− or minimal	>80 cell layers
Docetaxel	861.9	150–3000	− or minimal	1.5 mm
Antimetabolites				
5-Fluorouracil	130.1	117–1400	Minimal	0.5 mm
Gemcitabine	299.6	791–847	±	NA

AUC, Area under concentration versus time curve; *AUC ratio*, peritoneal fluid AUC/systemic AUC; *NA*, no data available.
[a] *AUC ratio of 4 for its active metabolite SN-38.*
[b] *±, contradictory results in experimental studies.*
Reproduced with permission from de Bree E, Michelakis D, Stamatiou D, Romanos J, Zoras O. Pharmacological principles of intraperitoneal and bidirectional chemotherapy. Pleura Peritoneum 2017;2:47–62.

autopsy findings showed that large parts of the visceral and parietal peritoneum displayed no stain or very little stain [36]. In particular, the hidden aspects of the cecum and stomach as well as large portions of the small and large intestines and of the diaphragm remained unstained. Our early experiments confirmed that distribution of methylene blue within the peritoneal cavity is poor after peritoneal lavage [37]. Recently, intestinal distribution of luminescent mRNA complexes was examined in a rodent model: the median small bowel luminescent surface was only about 10% after intraperitoneal injection of a liquid solution [15].

7. Pharmacological interventions to increase drug uptake

Drug uptake into peritoneal nodes can be influenced by pharmacological interventions. For example, hyperosmolar, highly concentrated therapeutic solutions can be administered with the hope of enhancing cytotoxic effect. However, this provides only limited additional advantage since in peritoneal tumor nodes, osmotic pressure is negligible compared to the interstitial fluid pressure [38]. Cancer cells within peritoneal metastases are therefore exposed to a lower effective concentration of therapeutic agent

than normal cells in the adjacent normal peritoneum, lowering the therapeutic efficiency and increasing toxicity. Administering vasoconstrictors such as epinephrine simultaneously with intraperitoneal chemotherapy reduces blood outflow and delays drug clearance from the subperitoneal space [39].

8. Role of formulation

During ontogenesis the peritoneum has acquired typical characteristics of an epithelium such as intercellular junctions, apical geometry, presence of microvilli, and secretion of a protective substance, the glycocalyx. The glycocalyx is an anionic, viscous barrier to fluid diffusion that protects the body against intraabdominal infection and tumor dissemination [40]. It is composed of glycosaminoglycans, in particular hyaluronan, a substance with high hydrophilicity that forms a hydrated gel polymer at the peritoneal surface [41]. Together with collagen, different cell types (fibroblast, adipocytes, and others), and blood and lymph vessels [42], hyaluronan is also a major component of the subperitoneal extracellular matrix. Degradation of hyaluronan thereby increases the permeability of the extracellular matrix and enhances the delivery of drugs and fluids through the extracellular matrix. Since hyaluronan has a rapid turnover [43], this effect is only temporary (for 12–24 h) [44]. Hyaluronidases are enzymes that can depolymerize hyaluronan by hydrolyzing the disaccharides and ultimately lead to hyaluronan degradation [45]. Hyaluronidases have been used for the last 70 years to modify tissue permeability through degradation of hyaluronan [46] and are approved in the United Kingdom for enhancing permeation of subcutaneous or intramuscular injections [47]. A recombinant hyaluronidase (rHuPH20) is approved by the Food and Drug Administration and was formulated for subcutaneous delivery with two anticancer therapies, trastuzumab and rituximab [48]. Although the effects have not been tested with intraperitoneal formulations, hyaluronidase might degrade the peritoneal glycocalyx and extracellular matrix, thus increasing tissue drug uptake through the peritoneal membrane.

9. Physical interventions to improve drug uptake

Experimental data support the potential benefit of increasing intraperitoneal hydrostatic pressure for increasing locoregional drug uptake. Increased intraabdominal pressure is thought to generate a convective flux that forces the drug from the peritoneal cavity into the subperitoneal tissue. Esquis et al. demonstrated in a rat tumor model that increasing the intraperitoneal pressure resulted in significantly higher cisplatin penetration in tumor tissue [49]. Similarly, Jacquet et al. found a significant enhancement of doxorubicin uptake in the abdominal wall and diaphragm of rats when the intraperitoneal pressure was increased to 20–30 mmHg [50]. In a swine model, intraabdominal high pressure enhanced diffusion of the drug in both the visceral and parietal peritoneum using a liquid solution [51].

Clinical applications of HIPEC with elevated intraabdominal pressure had so far been limited to palliating debilitating malignant ascites with laparoscopic HIPEC at 10–15 mmHg [52]. Recent data suggest that laparoscopic HIPEC (under a pressure of 12–15 mmHg) increases significantly tissue concentration of cisplatin as compared to open HIPEC [53]. This pharmacological advantage might explain the encouraging results documented after laparoscopic HIPEC for peritoneal metastasis of gastric origin [54]. The clinical use of intraabdominal pressure enhancement is indeed limited by respiratory and hemodynamic tolerance.

10. Specifications for an ideal intraperitoneal drug delivery system

A first for optimizing intraperitoneal drug delivery is to define the specifications of such an ideal system (Table 10.4).

Based on these specifications, we have proposed a new way of delivering intraperitoneal chemotherapy by application of cytotoxic drugs in the form of a pressurized aerosol into the abdominal cavity, pressurized intraperitoneal aerosol chemotherapy (PIPAC).

11. Peritoneal aerosol medicine

Therapeutic aerosols have been best investigated in detail in pulmonary medicine but there is little knowledge about using aerosols for intraperitoneal drug delivery. In principle, an aerosol is a suspension of particles in a gas. When applying therapeutic aerosols, it is useful to remember that they are subject to physical laws. These general laws, including size distribution, terminal velocity, aerodynamic diameter, dynamics and dynamics regime, partitioning, activation, and coagulation, are relatively complex and are described in detail elsewhere [55].

From a theoretical point of view, intraabdominal or intrapleural administration of therapeutic aerosols appears easier and more reproducible than pulmonary applications for the following reasons:

- Physical laws governing aerosol deposition are concerned principally with inertial impaction and gravitational sedimentation. Inertial impaction occurs chiefly in pulmonary medicine with larger particles whenever the transporting airstream is fast, changing direction, or turbulent (for example, in the oropharynx or at bifurcation between successive airway generations). Inertial deposition is therefore influencing aerosol delivery by capturing a significant part of the therapeutic substance in the upper airways. This problem does not exist within the peritoneal cavity, where deposition mainly follows gravitational sedimentation.
- One of the most critical maneuvers during pulmonary administration is to coordinate the actuation of the aerosol with the patient's inspiration. This problem does not exist during intraperitoneal administration.
- Gas molecules travel in random paths and collide with one another and the organ walls. These collisions exert a pressure per unit area

TABLE 10.4 Specifications for an ideal intraperitoneal drug delivery system.

Minimally invasive
Homogeneous drug distribution
Deeper drug tissue penetration
Higher local drug concentration, low systemic uptake
Can be repeated
Feasible in most patients
Simple and easy to perform
Cost effective
Preservation of quality of life
Objective assessment of tumor response

and also cause the gases to occupy a volume. Both pressure and volume are affected by temperature. The interrelationships between these three variables were formulated by Boyle, Charles, and Gay-Lussac [56], and can be applied to pharmaceutical aerosols. PIPAC allows modification of the intra abdominal or intrapleural temperature by applying cooled or heated CO_2, which is barely possible in pulmonary medicine.

Usually in aerosol medicine, an inert gaseous compound under pressure serves as a propellant for the therapeutic substance. The propellant serves several purposes:

- Pushing the product out of the can;
- Vaporizing after leaving the container, producing a spray or foam;
- Acting as a solvent for the product (in most cases).

Since the abdomen cannot be expanded indefinitely and since an open drug delivery system was not possible because of occupational health safety concerns, we selected a technological approach for intraperitoneal drug delivery that is radically different from the aerosol can technology established in pulmonary medicine.

12. Pressurized intraperitoneal aerosol chemotherapy

PIPAC relies on logical physical principles: local administration into the body cavity to improve therapeutic ratio, gaseous form to achieve homogeneous drug distribution, pressure application to enhance convective drug uptake into tumor nodes, and minimally invasive approach to minimize operative trauma. PIPAC allows repeated therapy cycles and objective tumor response assessment.

During minimally invasive surgery, pneumoperitoneum is applied to create a working space. This working space allows safe placement of access ports through the abdominal wall, outstanding visualization of organs, and completion of complex surgical procedures.

During a staging laparoscopy, an aerosol cytostatic agent is applied in the abdominal space using a nebulizer. Application as an aerosol allows the relatively even distribution of the substance. Increased pressure (12 mmHg) ensures deeper penetration into the tissue.

PIPAC (Fig. 10.1) is applied through laparoscopic access using two balloon trocars in an operating room equipped with laminar airflow. In a first step, a normothermic capnoperitoneum is established with a pressure of 12 mmHg. A cytotoxic solution (about 10% of a normal systemic dose) is nebulized with a micropump into the abdominal cavity and maintained for 30 min. The aerosol is then removed through a closed suction system.

In contrast to inhalers commonly used in pulmonary medicine, no propellant gas is needed, but during PIPAC a liquid solution is aerosolized into a gaseous (CO_2) environment, using a specific nozzle (Capnopen, Capnomed, Zimmern, Germany). Energy is provided by applying an upstream mechanical force gradient provided by an industry-standard angioinjector (e.g., Accutron HP, MedTron, Saarbrücken, Germany).

During PIPAC, an artificial pressure gradient is generated within the abdominal cavity that overcomes tumoral interstitial fluid pressure. This results in a higher local drug concentration compared to catheter-based intraperitoneal or intravenous chemotherapy. At the same time the plasma concentration of the chemotherapeutic agent remains low.

Applying an aerosol in the peritoneal cavity allows a relatively homogeneous distribution of the chemotherapeutic agent within the abdomen. Theoretical considerations suggest that the therapeutic capnoperitoneum should be capable of carrying microdroplets of active substances to all exposed peritoneal surfaces. These considerations were confirmed by several preclinical experiments, showing that the active

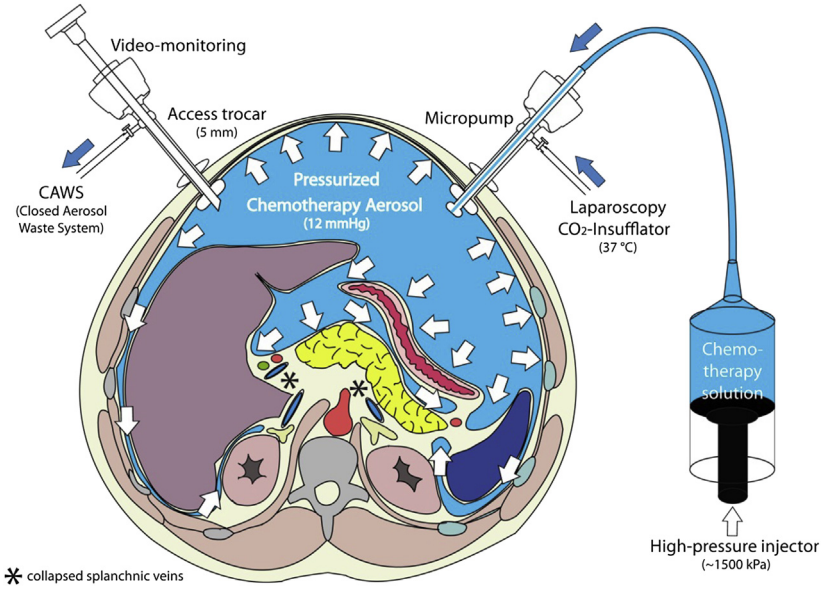

FIGURE 10.1 Principle of pressurized intraperitoneal aerosol chemotherapy.

principle is distributed relatively homogeneously throughout the abdomen, reaching exposed and even partially hidden surfaces.

The size of the aerosol particles has indeed a major influence on their behavioral properties, and the aerosol particle radius or diameter is a key property used to characterize aerosols. During PIPAC, the aerosol consists of a bimodal volume-weighted particle size distribution with a median droplet diameter of $\times 50.3 = 25$ μm Whereas the vast majority of droplets delivered during PIPAC have a diameter around 3 μm, over 97% of the volume of the aerosolized liquid is delivered as droplets of ≥ 3 μm in diameter. These larger droplets are primarily deposited on the surface beneath the nebulizer by gravitational settling and inertial impaction [57]. Current PIPAC technology allows aerosolizing solutions with higher viscosity, including polymers, glucoses, and lipids. Moreover, it has been shown to work in environments highly saturated with humidity. Whereas endoscopic microcatheters are able to spray aqueous solutions [58], they cannot reliably aerosolize polymer-based formulations with higher viscosity. Aerosolizers based on microperforated membranes did not function reliably with complex solutions or in environments saturated with humidity [59].

13. Electrostatic precipitation pressurized intraperitoneal aerosol chemotherapy

An embodiment of PIPAC is electroprecipitation of the therapeutic aerosol to improve homogeneity of spatial distribution and depth of tissue penetration. In addition, electrostatic precipitation pressurized intraperitoneal aerosol chemotherapy (ePIPAC) has the potential to shorten the operating time needed for application, and to reduce potential occupational health safety hazards. Electrostatic precipitation devices have been certified for clearing the visual field from surgical smoke during laparoscopy [60] and the same technology can be used for precipitating therapeutic aerosols. We first showed the in vivo feasibility of ePIPAC in swine [61]. Later

on, we treated terminally ill patients with ePIPAC without significant adverse events, and radiological tumor responses were observed [62]. Clinical results of a first cohort of peritoneal metastasis patients treated with 135 ePIPAC have been published. ePIPAC was well tolerated and safe. After three procedures and concomitant chemotherapy, response or stable disease was achieved in approximately half of cases [63]. ePIPAC with oxaliplatin is currently being investigated in a prospective trial in a homogeneous patient cohort with colorectal peritoneal metastasis [64].

Pressurized intraperitoneal aerosol chemotherapy consists of six key breakthrough qualities:

1. Adequacy of drug distribution throughout the entire peritoneal cavity
   If anticancer drugs cannot reach all the cells within a tumor, their effectiveness is compromised. Physical laws support the superior distribution of drugs within the abdominal cavity if they are administered in gaseous form, like during PIPAC, rather than in liquid form, like with intraperitoneal catheters.
2. Increased direct penetration of drugs
   PIPAC directly delivers chemotherapy under pressure, increasing tissue penetration and inducing the regression of peritoneal tumor nodes up to several millimeters. This is a clear advantage over other delivery routes such as HIPEC.
3. Decrease in the outflow of drug from the tumor by capillary flow
   PIPAC reduces blood outflow from the abdomen over the liver and the abdominal wall during the uptake phase. This increases the pharmacokinetic advantage of regional delivery and limits toxicity.
4. Repeated application
   PIPAC allows repeated local application of chemotherapy for up to a maximum of nine sessions. At the beginning, therapy intervals are 6 weeks; in the case of objective tumor regression this can be prolonged to 3 or even 6 months. This is another advantage over HIPEC.
5. Toxic effects associated with local delivery
   Advanced peritoneal cancer patients generally suffer gastrointestinal symptoms that deteriorate until death. Analysis of quality of life data showed that gastrointestinal symptoms remained stable following PIPAC. Global quality of life improved and disease-related symptoms were stabilized for several months in the majority of patients.
6. Added time, inconvenience, and cost
   Although it is not yet possible to balance patient benefits of PIPAC against costs for the healthcare system, it is feasible to say that PIPAC is a minimally invasive procedure requiring a short hospital stay. The costs of chemotherapy are much lower than systemic palliative chemotherapy.

14. Chemotherapeutic agents used as PIPAC

PIPAC is a generic drug delivery technique allowing distribution of a large range of substances, including the following.

14.1 Oxaliplatin

For peritoneal metastases of colorectal cancer and for appendix cancer, intraperitoneal oxaliplatin was administered at an arbitrary dosage of 92 mg/m^2 body surface [65]. This dosage was derived from a HIPEC dosage that had been reduced by 80% [66]. Two dose-finding studies are currently being conducted to determine the optimal dosage of oxaliplatin [67,68]. Results of one of these studies have been presented and confirmed the arbitrary dosage of 92 mg/m^2, significant toxicity having been observed at a dosage of 140 mg/m^2 [67]. Some patients have experienced major or even complete histological response allowing a secondary complete resection. This observation has to be contrasted with the absence of efficacy of additional HIPEC with oxaliplatin 460 mg/m^2 observed in the PRODIGE 7 trial and are a further argument for the pharmacological superiority of PIPAC over HIPEC as a drug delivery system.

14.2 Cisplatin and doxorubicin

For all other indications (ovarian [69], stomach [70], mesothelioma [71], hepatobiliary [72], and pancreatic [73,74] tumors), a combination of low-dose doxorubicin and cisplatin is currently used. The defined dosage after a dose-escalation study for doxorubicin is 2.1 mg/m^2 body surface and for cisplatin a 10.5 mg/m^2 body surface [75]. Comprehensive clinical reports on the use of these substances have been published [76] and reviewed [77].

14.3 Nab-paclitaxel

The use of nab-paclitaxel (Abraxane) as PIPAC is currently being studied in a phase I–II trial in patients with gastrointestinal and ovarian peritoneal metastases [78]. Previously, intraperitoneal catheter-based delivery of nab-paclitaxel was studied in a phase I trial in patients with advanced peritoneal metastasis [79]: the maximally tolerated dose of intraperitoneal nab-paclitaxel was 140 mg/m^2; dose-limiting toxicities included CTCAE ≥ 3 neutropenia and abdominal pain. Over the four dose levels, the peritoneal/systemic ratio (AUC_{ip}/AUC_{plasma}) was ~150-fold with low intrapatient variability. These clinical data confirmed previous preclinical studies demonstrating that intraperitoneal administration of nano- and microsized formulations of paclitaxel resulted in superior antitumor activity against mouse ovarian cancer xenografts compared to intravenous administration [80]. For example, using a HIPEC model in the rabbit, peritoneal tissue concentrations after intraperitoneal administration of nab-paclitaxel were five times higher compared to intraperitoneal paclitaxel [81].

14.4 Caelyx

The first clinical data on intraperitoneal administration of pegylated liposomal doxorubicin (PLD) as PIPAC are available. The pharmacokinetics of conventional doxorubicin ($n = 10$ PIPAC) at a dose of 1.5 mg/m^2 were compared with PLD ($n = 15$ PIPAC) at the same dose. No traces of doxorubicin were found in the systemic circulation. Doxorubicin local tissue concentration was higher for the doxorubicin solution compared to PLD. In both cases, the drug accumulated in the abdominal cavity tissues without reaching the systemic circulation, supporting previous reports on the superior pharmacological properties of PIPAC and providing the rationale for the absence of systemic adverse effects [82]. These results build on previous ex vivo

data showing that depth of tissue penetration of PLD as PIPAC is inferior to doxorubicin in normal swine peritoneum [83].

14.5 Irinotecan

A small retrospective series of six patients treated with irinotecan 20 mg/m^2 as ePIPAC has been published [63]. No pharmacological data were provided.

15. Preclinical studies

Administration of the following agents as PIPAC was evaluated in preclinical models.

15.1 Paclitaxel

Results of a dose-escalation study in swine have been presented: paclitaxel was first administered as PIPAC at the starting dose of 60 mg/m^2; the same dose was administered 1 week later intravenously and pharmacokinetics data compared. Both plasma and tissue paclitaxel pharmacokinetic results support that PIPAC paclitaxel shows a linear pharmacokinetic property. Systemic exposure to paclitaxel was lower when administered via PIPAC compared to intravenous infusion. A favorable toxicity profile was seen with PIPAC paclitaxel, particularly at lower doses [84].

15.2 siDNA

Solass et al. examined the aerosolization of small inhibitory DNA (AsiDNA) as PIPAC ex vivo [85] and in swine [86]. AsiDNA is a short, noncoding, double-stranded, DNA-mimicking mutation. AsiDNA activates cellular DNA repair, preventing recruitment for repair of DNA mutations in cancer cells. Healthy cells acquire a competitive advantage over cancer cells, which will continue dividing with damaged DNA, ultimately leading to cell death [87]. This technology, first developed by Marie Dutreix from Institut Curie in Paris, might be interesting for potentializing the effect of radiotherapy and/or chemotherapy on peritoneal metastasis.

15.3 siRNA

RNA interference is another potential therapeutic approach for the treatment of peritoneal metastasis, and this approach has been pioneered by K. Remaut in Gent. Her group first showed in vitro that aerosolization of siRNA complexes does not significantly lower transfection efficiency [88] and that mRNA lipoplexes can withstand the high pressure applied during the PIPAC procedure. In a further step, using luciferase-coding mRNAs, they documented a superior spatial distribution of bioluminescence after PIPAC, as compared to intraperitoneal injection, while intravenous injection mainly induced protein expression in the spleen [15]. These seminal studies open the way for distributing siRNA and mRNA complexes in the peritoneal cavity during a PIPAC procedure.

16. Combination of PIPAC with systemic chemotherapy

In most treatment centers, PIPAC is also administered in combination with systemic chemotherapy [76]. Experience shows that this treatment combination is well tolerated [75,89,90]. Systemic chemotherapy is generally paused 2 weeks before PIPAC, but can be restarted shortly afterward [76]. Independently of a combination of PIPAC, angiogenesis inhibitors carry some risk of bowel perforation [91]. A combination with systemic administration of angiogenesis inhibitors has been reported to be safe [92]. However, there is a single case of bowel perforation after the combination of PIPAC with

bevacizumab in the international PIPAC register (www.clinicaltrials.gov, NCT03210298, data on file). Thus a pause of 4 weeks between last administration of bevacizumab and PIPAC is recommended.

17. In silico modeling

Knowledge of the peritoneal tissue, cancer-related modifications of this tissue, pharmacodynamics and pharmacokinetics characteristics, and available clinical experience highlight current limitations of intraperitoneal chemotherapy. To overcome these limitations, a better understanding of the uptake of a drug by peritoneal metastasis and of the drug's subsequent spatiotemporal distribution is needed [93]. Drug uptake and distribution are indeed dependent on the substance to be administered. These multiple, interdependent parameters can barely be tested in bench experiments and simulations might facilitate and speed up this research considerably. In silico modeling offers the possibility to test different protocols or drug formulations for intraperitoneal delivery, might provide unique insights into the effect of modifying factors on peritoneal drug uptake, and will limit the need for in vivo experiments (reviewed in Ref. [29]). To be most effect, such simulations must be supported by bench data, for example, high-resolution optical imaging of tumor tissue from animal models. Such in vivo imaging of vascular perfusion will visualize the uptake of therapeutic agents, as well as their spatiotemporal distribution within tumors [93].

18. Conclusion and outlook

While PIPAC is still in its infancy, its pharmacological superiority over systemic delivery for treating peritoneal metastasis is already clear—supported by in vitro, ex vivo, animal model, and clinical data. Able to induce regression of chemoresistant peritoneal metastasis, it meets the clinical need for new and better therapies for a fatal cancer.

As a generic drug delivery technology, PIPAC has potential applications for other pathologies. PIPAC is currently being tested in different types of cancer and parts of the body, while using different drugs. Following demonstrations of efficacy in the abdominal cavity, new intrathoracic applications are under development, paving the way for new treatments for mesothelioma [71], another rare form of cancer that commonly develops in the lining of the lungs. Indeed, the opportunities are vast. Since a therapeutic aerosol can also be distributed within organ cavities, applications, including pressurized intravesical aerosol chemotherapy for bladder cancer [94], or intraluminal endoesophageal applications for Barrett's dysplasia [86], are also under investigation. It may also be possible to use pressurized aerosols to improve the efficacy of radiotherapy [85] and to administer siRNA and mRNA [88], or even cellular therapies [83], to enhance efficacy of intraperitoneal therapy of peritoneal metastasis. PIPAC opens the door of the surgical field to pharmaceutical, physical, and biological tools and might become a game-changer [95] in the therapy of peritoneal metastasis.

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