1 The Basis of Regional Therapy, Pharmacology, Hyperthermia, and Drug Resistance

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The Basis of Regional Therapy

The peritoneal surface is a common failure site for most gastrointestinal and gynecologic malignancies, providing a strong incentive for studying regional approaches to chemotherapy delivery. The relative accessibility of the peritoneal cavity is another reason intraperitoneal chemotherapy, either as part of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) or as catheter-based repeated instillations, is the most commonly studied form of regional therapy.

The Peritoneal-Plasma Barrier

Intraperitoneally administered chemotherapy (IPC) enters the systemic circulation either by diffusion into the vascular compartment or by absorption through peritoneal lymphatics.

The rationale for this route of administration is based on the knowledge that the peritoneal membrane acts as a relative transport barrier between the peritoneal cavity and the systemic circulation. Contrary to intuitive thinking, resection of the mesothelial lining, like is done during peritonectomy in cytoreductive surgery, does not seem to affect transport of agents between the peritoneal cavity and the systemic circulation. This was shown by Flessner et al. in 2003 who demonstrated that neither removal of the stagnant peritoneal fluid layer nor resection of the mesothelial lining influenced the mass transfer coefficient (MTC) in a rodent model [1]. Similarly, the extent of parietal peritonectomy does not seem to influence IP chemotherapy pharmacokinetics in humans [2–5]. This is explained by the fact that the principal barrier for clearance of solutes from the abdominal cavity consists of the submesothelial blood capillary walls and the surrounding ECM rather than the mesothelial lining.

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Compartment Model for IP Drug Delivery

The tissue surrounding the peritoneal cavity can absorb almost all agents [6, 7]. Subperitoneal tissues mediate the transfer of IP fluid and solutes via lymphatics or blood flow into the circulation. Even though within 24 hours the entire peritoneal surface will make contact with an IP-administered solution, only a fraction (approximately 30%) is typically in contact at any given time. The volume of the solution, adhesions, the size of the patient, and the patient's position all affect the peritoneal contact area. Pharmacologic studies of IP chemotherapy typically simplify this complex clinical situation by considering the peritoneal cavity to be a single compartment separated by an effective membrane (peritoneum) from another single compartment, plasma [8]. Fick's law of diffusion to transperitoneal transport can be applied. Transfer of a drug from the peritoneal to the systemic circulation occurs across the peritoneal membrane, governed by the permeability-area product (PA). The latter is calculated by measuring the rate of drug disappearance from the cavity divided by the overall concentration difference between the peritoneal cavity and plasma.

$$\text{Rate of mass transfer} = \text{PA}\left(\text{CP} - \text{CB}\right).$$

The importance of the effective contact area is highlighted this way, but its value in actual transfer across the membrane is not determined in this model.

Dedrick Diffusion Model

The pharmacokinetic rationale for IPC is based on "dose intensification" achieved by the peritoneal-plasma barrier [9]. Dedrick et al. concluded from peritoneal dialysis research that the peritoneal permeability of a number of hydrophilic drugs may be considerably less than their plasma clearance [10]. After IP administration, peritoneal clearance is inversely proportional to the square root of the drug's molecular weight. Once the drug enters the systemic circulation, it undergoes rapid metabolism limiting its systemic toxicity. This leads to a significantly higher concentration in the peritoneal cavity compared to the plasma. Simplified, this means that when the concentration of intraperitoneally administered drug in the peritoneal solution is plotted over time, the area under the curve (AUC) provides an idea of the efficacy of the treatment. On the other hand, when after IP administration of chemotherapy its IV concentration is plotted over time, the AUC will provide an idea of the toxicity of the treatment. The difference in drug concentration between the peritoneal cavity and the systemic circulation attributed by the peritoneum-plasma barrier has been called the pharmacokinetic advantage. This dose intensification is expressed as the AUC ratio of intraperitoneal (IP) versus plasma (IV) concentrations. Practically, this means that after CRS, this concentration difference enables exposure of residual tumor cells to high doses of chemotherapeutic agents, while reduced systemic concentrations limit systemic toxicity.However, two important factors must be taken into consideration regarding this simplified model. Firstly, exposure of residual tumor cells to increased drug levels by increasing drug concentration at their surface (achieved by changing pharmacokinetic variables) does not necessarily lead to increased uptake and thus high intratumoral concentration. The ideal drug for IP administration should not only be retained in the peritoneal cavity for a prolonged period but also be able to penetrate in high concentrations into tumoral tissue.

Secondly, recent publications indicate factors other than systemic absorption may influence the AUC ratio such as the timing of the last measurement of plasma AUC, the instillation time, and the grade of drug distribution in the body (the distribution of drug into the peripheral compartment) [11]. The latter has also been shown by Lemoine et al. who observed an additional peak in the plasma AUC with elongation of measurements after IP instillation due to remobilization of the drug out of the peripheral compartment.

Peritoneal Carcinomatosis: Changed Barriers

Malignant invasion of the peritoneum often causes at least partial destruction of the normal peritoneum. This results in lack of a mesothelial layer over the tumor, an altered interstitium, hyperpermeable microcirculation, and the lack of lymphatics which can all affect intraperitoneal chemotherapy.

Neoplastic Peritoneum

The loss of mesothelial cells in the neoplastic peritoneum leads to lack of a smoothly gliding peritoneal surface, promotes formation of adhesions, and decreases the function of the immune system. Furthermore, it allows macromolecules to pass through. This has been shown by the ability of viral vectors containing antisense RNA to penetrate through cancerous peritoneum but not normal peritoneum [12].

Lymphatics

In peritoneal carcinomatosis, the subdiaphragmatic as well as the visceral lymphatics may be obstructed, leading to disturbed protein clearance and ascites [13, 14]. Supradiaphragmatic lymph nodes may be overwhelmed by tumor cells, providing a metastatic route to the systemic circulation. However, if these pathways are still functional at the time of IP therapy, they may provide a direct route for the drug into the systemic circulation (especially in case the drug has a molecular weight greater than that of albumin).

Tumor Microenvironment

The tumor microenvironment consists of two components: the extracellular fluids (blood, lymph, interstitial fluid) and solids (connective tissue proteins and mucopolysaccharides). The fluids are subdivided into the vascular and the interstitial space, separated by the vascular wall. A tumor can thus be seen as a three-compartment model consisting of the malignant cells, the vessels, and the interstitial water space.

Microvasculature

The normal capillary wall consists of the endothelium lined by a glycocalyx which is more pronounced at the level of interendothelial clefts to provide passage to only small molecules (e.g., insulin 5500 Da). Elsewhere, a limited number of gaps with less dense glycocalyx exist to permit protein leakage [15]. It is the glycocalyx surrounding the endothelium that provides most of the barrier to solute transfer. Inflammation and certain drugs can cause degradation of the glycocalyx, thereby increasing the capillary permeability [16]. Furthermore, neo-angiogenesis that accompanies malignancy results in the formation of vessels that contain no or minimal glycocalyx and are unevenly distributed [17]. Although these leaky neo-capillaries might provide rapid clearance of drugs from the systemic circulation into the tumor, the high interstitial pressures limit effective drug penetration.

Interstitium

Alterations in the interstitial pressure change the interstitial water space and thus the tissue available for solute transport [18]. It has been shown that the malignant interstitium is markedly expanded in comparison to the interstitial water space of normal tissue [17, 19]. Despite this, malignant interstitium seems to be more resistant to transfer of molecules compared to normal interstitium. Furthermore, an increased interstitial water space implies a greater distance between the vessels and tumor cells contributing to “metabolic death” and difficulty of IP chemotherapeutic to get access to malignant cells. The malignant interstitial pressure can reach up to 45 mmHg, with increased pressures present

within the first millimeter of tumor tissue below the peritoneal surface which limits convection of IP drugs [15–20]. The upper limit of IP pressure tolerated by an ambulatory patient is 8–10 mmHg. Anesthetized and mechanically ventilated patients can tolerate higher IP pressures; however, values >15 mmHg might impair portal circulation or respiration [17, 20–22].In conclusion, multiple characteristics of the neoplastic interstitium may negatively impact the ability of intraperitoneal drugs to reach and penetrate malignant cells.

Pharmacology

The pharmacology of IP chemotherapy can be subdivided into pharmacokinetics and pharmacodynamics. Pharmacokinetics evaluates what the body does to the drug by analyzing what happens between the moment of administration of the IP chemotherapy and the drug showing up at the level of the tumor nodule. Pharmacodynamic studies focus on delivering the chemotherapy in the most efficient way possible at the level of the tumor nodule. Concentration over time graphs is used for illustration of pharmacokinetic properties. Pharmacodynamics describe what the drug does to the body, looking at the effect the chemotherapy really has on the tumor illustrated by effect over concentration graphs. Table 1.1 summarizes the most important Pk and Pd variables characterizing pharmacology of IPC.

Table 1.1 Pharmacokinetic and pharmacodynamic variables of IPC

Pharmacokinetic variables (Pk)	Pharmacodynamic variables (Pd)
Dose	Temperature
Volume	Size residual tumor nodule
Duration	Density
Carrier solution	Binding
Pressure	Interstitial fluid pressure
Vasoactive agents	Charge
Macromolecular vehicles	Vascularity

Pharmacokinetics

Dose: BSA-Based Versus Concentration-Based

Due to the multitude of perioperative cancer therapy centers worldwide, different schedules of chemotherapeutic agents, concentrations, and doses have been developed. The current dosing regimens of IP chemotherapy can be divided into body surface area (BSA)-based and concentration-based.

Most groups use a drug dose based on calculated BSA (mg/m2) in analogy to systemic chemotherapy regimens. These regimens take BSA as a measure for the effective peritoneal contact area. However, Rubin et al. demonstrated there is an imperfect correlation between actual peritoneal surface area and calculated BSA [23]. Furthermore, females have a 10% larger peritoneal surface in relation to their body size which probably affects absorption. BSA-based IP chemotherapy will result in a fixed dose (BSA-based) diluted in varying volumes of perfusate, implicating different concentrations. From the Dedrick formula, we know that peritoneal concentration and not peritoneal dose is the driving diffusion force. The importance of this finding has been discussed by Elias et al. in a clinical investigation where 2, 4, and 6 liters of chemotherapy solution were administered with a constant dose of chemotherapy solution [24]. A more dilute IP chemotherapy concentration retarded the clearance of chemotherapy and resulted in less systemic toxicity [25]. Therefore, it can be assumed that by the diffusion model, less concentrated chemotherapy would penetrate to a lesser extent into the cancer nodules and normal tissues. To increase the accuracy of predicting systemic drug toxicity, the volume of chemotherapy solution should also be determined by the BSA, resulting in a constant chemotherapy dose as well as its concentration.

Some groups use a dosimetry regimen based on concentration. The total amount of chemotherapy is mixed in a large volume of carrier solution. This regimen offers a more predictable

exposure of the tumor nodules to the IP chemotherapy by maintaining a constant diffusional force and thus cytotoxicity. Unfortunately, this also leads to unpredictable plasma chemotherapy levels and thus toxicity [11].

Currently, there is an ongoing randomized trial evaluating the pharmacology and morbidity of both dosing methods, entitled "concentration-based versus body surface area-based perioperative intraperitoneal chemotherapy after optimal cytoreductive surgery in colorectal peritoneal carcinomatosis treatment: randomized non-blinded phase II clinical trial" (COBOX trial) NCT03028155.

Volume

Target lesions or residual microscopic malignant cells can be present anywhere on the peritoneal surface and ideally should be reached by the chemotherapy solution during HIPEC. However, not only the body composition of the patients but also the methods of HIPEC administration (open versus closed) as well as determination of the perfusate volume (chosen arbitrarily, BSA-based, standard 2, 4, or 6 l) differ greatly. As descried in the previous paragraph, administration of variable volumes until the abdomen is full, to increase the contact area, is not a recommended practice due to the risk of over- or under-dosing, leading to unpredictable systemic toxicity.

Duration

After a drug is administered intraperitoneally, tumor cell kill will increase with time of instillation until it reaches its maximum effect at a certain moment, after which prolongation of the exposure will not offer any further cytotoxic advantage. Gardner et al. mathematically modeled dose-response curves and their dependency on exposure time [26]. Since a plateau in tumor cell kill is reached at a certain time, the most advantageous exposure time for IPC should be carefully weighed against accompanying systemic toxicity. Based on this rationale and understanding, depending on the drug used, the duration of HIPEC ranges from 30 to 120 minutes. However, the duration of IPC should be pharmacology-driven and not arbitrary.

Carrier Solution

The choice of carrier solution to deliver IPC has an impact on its efficacy and toxicity. Hypotonic, isotonic, and hypertonic solutions were explored with both low and high molecular weight chemotherapy molecules. The ideal carrier solution should provide the following: enhanced exposure of the peritoneal surface, prolonged high intraperitoneal volume, slow clearance from the peritoneal cavity, and absence of adverse effects to peritoneal membranes [27]. This is especially important in the setting of EPIC where maintenance of a high dwell volume of chemotherapy solution over a prolonged time period improves the distribution of the drug and the effectiveness of the treatment [28]. Mohamed et al. showed that an isotonic high molecular weight dextrose solution would prolong the intraperitoneal retention of the artificial ascites [29]. Several in vitro and animal studies suggested a pharmacokinetic advantage of hypotonic carrier solutions in a HIPEC setting [30, 31]. Elias et al. studied the pharmacokinetics of heated oxaliplatin with increasingly hypotonic carrier solutions in colorectal PC patients [32]. They reported no significant differences in absorption and intratumoral oxaliplatin but a very high incidence of unexplained postoperative bleeding (50%) and unusually severe thrombocytopenia in patients treated with hypotonic carrier solutions. Furthermore, oxaliplatin was initially considered unstable in chloride-containing media, resulting in the use of 5% dextrose as its carrier solution. This was based on extrapolation of systemic chemotherapy data. However, exposure of the peritoneum to 5% dextrose during perfusion times varying from 30 to 90 minutes is associated with serious hyperglycemia and electrolyte disturbances, resulting in significant added postoperative morbidity and mortality. Subsequent HIPEC-specific data demonstrate no such instability [33]. Furthermore, this degradation of oxaliplatin in normal saline only accounts for

less than 10% of the total amount at 30 minutes, as when applied during HIPEC. Moreover, oxaliplatin degradation was associated with the formation of its active drug form [33, 34].

Pressure

An increase in the intraperitoneal pressure causes increase of the extracellular space in the interstitium of the peritoneum, leading to increased effective tissue diffusivity [1, 8]. This can be derived from the Dedrick et al. formula postulating that the depth of drug penetration is equal to the square root of the ratio of tissue diffusivity and the rate constant for drug removal from the tissue, together with Flessner et al. describing an increase in the extracellular space due to increased IP pressure. Several animal models have confirmed these findings of increased intratumoral accumulation and cytotoxicity of drugs like cisplatin, oxaliplatin, and doxorubicin [8, 35–37]. However, the useful application of increased intra-abdominal pressure is limited by respiratory and hemodynamic intolerance. Proponents of the closed delivery method of HIPEC use the increased pressure of administration as one of the advantages over the open/coliseum technique (apart from less heat loss and a reduced chance of safety hazards). Currently, there are two clinical applications of administering IPC at raised IP pressure, being laparoscopic HIPEC (at 12–15 mmHg) and pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Vasoactive Agents

There has been a lot of interest in the use of vasoactive substances to regulate peritoneal and tumor blood flow [8, 38–43]. Vasoconstricting agents may contribute to delayed clearance of the IPC since it is known that blood flow through the (sub-)peritoneal network plays an important role in the movement of fluids and solutes across the peritoneal barrier. Duvillard et al. observed better survival in a rat model in the animals treated with IP adrenaline and cisplatin compared to those treated with cisplatin alone [44]. The safe combination of IP adrenalin and cisplatin was shown in 18 patients by Loucon-Chabrot et al [43] In addition, Facy et al. showed adrenaline to be more effective than hyperthermia in increasing intratumoral drug concentrations of cisplatin in a rat model [40]. Lidner et al. observed a pharmacokinetic advantage of adding intravenous vasopressin administration to IP carboplatin and etoposide but not to 5-FU [42]. Considering very limited clinical experience, further studies on the routine used of these agents together with IPC as an attempt to improve effectiveness are required before its routine use.

Timing of IPC Administration in Relation to the Surgical Intervention

The most commonly used method of perioperative delivery of intraperitoneal chemotherapy is hyperthermic intraperitoneal chemotherapy (HIPEC). However, the application of IPC in clinical practice can occur at four timepoints which may have some impact on its effects.

Induction or Neoadjuvant IPC

In an attempt to reduce intraperitoneal disease burden and potentially test the response to the chemotherapeutic agent, IPC can be administered before definitive surgical cytoreduction. This could theoretically facilitate the surgery or increase the likelihood of complete cytoreduction. Radiological and clinical responses to neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) in gastric cancer have been reported [45–47]. Possible disadvantages may include adhesions, extensive fibrotic response to IPC, and increased morbidity at the time of cytoreduction and HIPEC due to previous direct chemotherapeutic exposure. Further studies on the effectiveness of NIPS are warranted and currently under way for colon cancer.

Intraoperative

HIPEC is the most commonly adopted method in which heated IPC is administered immediately after surgical cytoreduction. The advantage of this method is the fact that tumor load and adhesions are minimized, increasing the likelihood of even distribution and exposure to IPC.

A subtype of HIPEC is bidirectional intraperitoneal chemotherapy (BIC)administration. Elias et al. first described the supplementation of IV

chemotherapy to IP chemotherapy to improve the cytotoxic efficacy [33]. The IV chemotherapy (5-FU) is given simultaneously or immediately prior to (15, 30, or 60 minutes) HIPEC. Within approximately 20 minutes, the peritoneal fluid becomes saturated with 5-FU, known as "pharmacologic sink phenomenon." Subsequently, this drug can only leave the peritoneal space by back diffusion. Due to rapid metabolization, only occurring in the liver and gastrointestinal tract mucosa, marked differences in peritoneal and plasma concentrations appear, which makes 5-FU an ideal drug for intraperitoneal administration with limited systemic effect [48, 49].

Early Postoperative Intraperitoneal Chemotherapy (EPIC)

After CRS with or without HIPEC, four drains and one Tenckhoff catheter are left in the abdomen. During the first 3–5 postoperative days, the abdominal cavity remains free from adhesions, and thus, a normothermic chemotherapeutic infusion can be instilled directly into the peritoneal cavity as a 23-hour dwell. In the treatment of CRC and appendiceal mucinous neoplasms, 5-FU is the most commonly used agent for this purpose because of its pharmacokinetic advantages. Given its cell-cycle-dependent activity, this is an ideal drug for repeated exposure. Furthermore, it is a small molecular weight molecule that moves rapidly out of the peritoneal cavity to the plasma where it is even more quickly metabolized by an enzyme that is only present in the liver and gastrointestinal tract mucosa, thereby lowering systemic toxicity. Paclitaxel has a favorable pharmacologic profile and mechanism of action for EPIC and is used for ovarian cancer and mesothelioma [50].

Pharmacodynamics

Until fairly recently, the pharmacologic efficacy of IPC was assessed by looking at the pharmacokinetics of the IP and IV compartment [51, 52]. However, Van der Speeten et al. in 2009 demonstrated a higher intra-tumoral doxorubicin concentration that could be predicted by simple IP/IV pharmacokinetics [53]. The penetration of cytotoxic drugs into the target peritoneal tumor nodules is a complex, multistep process dependent on multiple factors.

Density of the Tumor Nodules

In 2009, Van der Speeten et al. observed that the amount of doxorubicin measured in less dense diffuse peritoneal adenomucinosis (DPAM) subtype of appendiceal mucinous neoplasms was statistically significantly lower than in the denser peritoneal mucinous carcinomatosis nodules (PMCA) despite the same exposure to intraperitoneal drug [53].

Tumor Nodule Size

Results from experiments with multicellular models have shown that direct tissue penetration of most cytotoxic agents is very limited in space, four to six cell layers in doxorubicin, 0.5 mm in 5-FU, and maximally 2–5 mm in mitomycin C [52]. IPC effectiveness will therefore be limited to tumor nodules of a very small dimension. Since human cancers are known to obey the so-called Gompertzian growth kinetics, the presence of small tumor nodules will result in an additional advantage related to the population kinetics of tumor growth. This growth kinetics implies that instead of a continuous exponential growth, a plateau is reached when nutrient and oxygen supply no longer meet demands, resulting in a decline in growth when the tumor size increases. Small tumor nodules will have the largest growth fraction, and therefore, the fractional kill by chemotherapy will be much higher than later in the course of the disease [51].

Hyperthermia

The addition of hyperthermia to IP chemotherapy has been postulated to increase its effectiveness by several mechanisms. First, a direct antitumor effect of heat due to increased cell death has been reported. Mild hyperthermia seems to be selectively cytotoxic to malignant cells due to impaired DNA repair, protein denaturation, and inhibition of oxidative metabolism in the microenvironment of malignant cells, leading to increased acidity, lysosomal activation, and increased apoptosis

[54, 55]. Second, heat seems to work synergistically with selected drugs (doxorubicin, MMC, melphalan, platinum, docetaxel, gemcitabine, irinotecan) augmenting their cytotoxic effect by inhibition of intracellular detoxification pathways, disturbing DNA repair mechanisms, and damaging ATP transporters, leading to drug accumulation [56]. Finally, hyperthermia could increase penetration of chemotherapeutic agents in normal as well as malignant tissues [57].

Multiple experimental studies have investigated the role of heating various IP chemotherapeutic agents. Piché et al. studied the effect of heat on IP-administered oxaliplatin in Sprague-Dawley rats. Besides increasing plasma concentrations of the drug proportionally to the IP-administered dose, they showed that heat not only enhanced peritoneal tissue concentration but also decreased its systemic absorption [58]. Concerning the effect of hyperthermia on IP-administered taxanes (paclitaxel and docetaxel), Muller et al. performed an in vitro study on human ovarian carcinoma cell lines but failed to observe any positive effect of heating these agents. Since other publications on heated taxanes have shown conflicting results, more studies on this matter are required [59]. The same lack of evidence exists for heating of IP mitomycin C. Klaver et al. randomly performed CRS, CRS/HIPEC, CRS with normothermic chemotherapy, and CRS with heated saline on WAG/Rij rats. They demonstrated the effectiveness of IP chemotherapy administration (normo- or hyperthermic) but failed to show any beneficial effect of hyperthermia [60]. However, hyperthermia exceeding 42 °C has been demonstrated to have a direct cytotoxic effect on normal as well as tumor cells [61, 62]. Sorensen drew the same conclusion after investigating the difference between normothermic and hyperthermic IP MMC administration in a rat model [63]. Further research in this area is mandatory before omitting this part of the procedure. However, since hyperthermia can be a logistic reason complicating widespread use of IP chemotherapy in many parts of the world, the suggested increased cytotoxicity of adding hyperthermia to IP chemotherapy observed by basic science needs urgent validation in clinical trials.

Drug Resistance

For chemotherapeutic agents to effectively kill malignant cells, the agents must first reach the target. The inability of the drug to reach the target is a basic mechanism of drug resistance that affects both intravenously and intraperitoneally administered agents. For targets on the peritoneal surface, IP administration allows dose intensification providing high concentrations of therapeutic agent right at the level of the tumor providing a better opportunity to reach the target.

However, as previously discussed, the high concentration of drug at the peritoneal surface and the AUC ratio itself may not directly translate into increased penetration to the tumor cellular level, and therefore, analysis specific to the tumor tissue itself is needed. This was emphasized in the following experiment: when comparing the AUC plasma, peritoneum, and tumor nodule curves for different chemotherapeutic agents used in the treatment of peritoneal carcinomatosis, differences in drug concentration within the tumor nodules of doxorubicin, cisplatin, or melphalan were observed despite the same peritoneal AUC curve (Fig. 1.1). Furthermore, Van der Speeten et al. observed a higher intra-tumoral doxorubicin concentration than could be predicted by simple IP/IV pharmacokinetics [53] (Fig. 1.2).

Another reason to use the tumor nodule as the pharmacological endpoint is provided by the finding of Van der Speeten et al. in their analysis (HPLC plasma, urine, and peritoneal fluid) of 145 peritoneal carcinomatosis patients treated with mitomycin C [5]. Mitomycin C is not a prodrug but is modified to its active state after entering the tumor cell. In 6 of these 145 patients (4%), the HPLC chromatogram showed no evidence of mitomycin C metabolites, suggesting that MMC was not metabolized in these patients. The patients had the same clinical and surgical factors as the other 139 patients, and until now, there is no known genetic or metabolic reason for this phenomenon. This might be an example of absolute drug resistance.

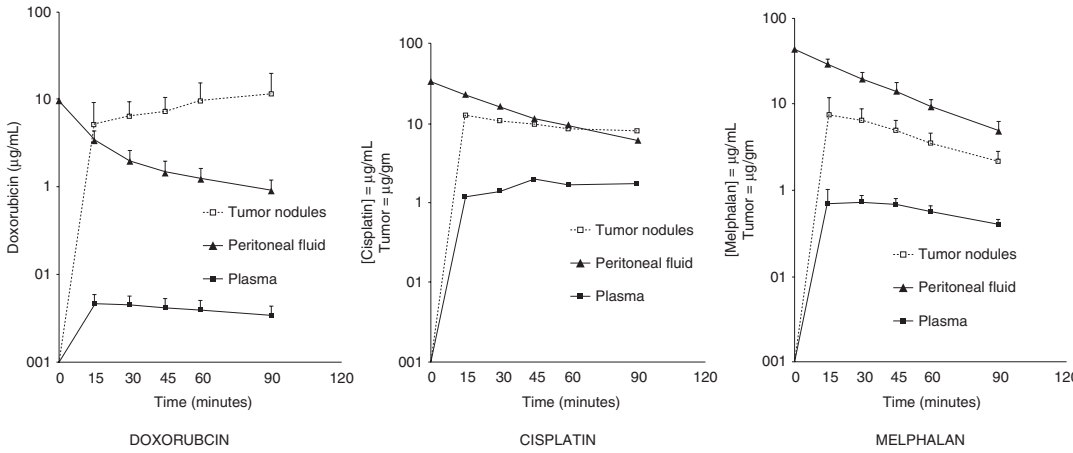

Fig. 1.1 Comparison of AUC of different IPC drugs

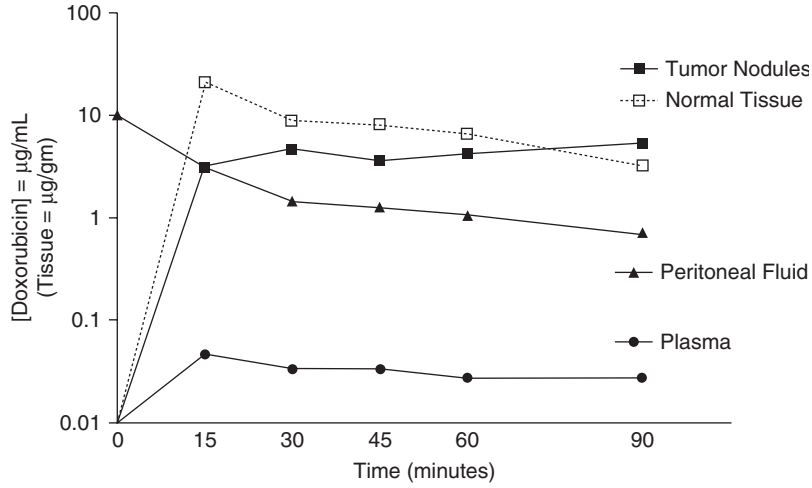

Fig. 1.2 Doxorubicin concentrations in plasma, peritoneal fluid, tumor nodules, and normal adjacent tissue in one patient

How to Select the Right IP Drug

Traditionally, the selection of drugs for intraperitoneal administrations has been based on beneficial pharmacokinetic and pharmacodynamic parameters, a good tolerance profile, and proven effectiveness with systemic administration as described in the previous paragraphs. However, the value of these parameters to predict what level of drug will be reached at the tumor cell level is likely limited. Furthermore, a more specific and personalized analysis of potential chemosensitivity aiming at increased effectiveness and limited toxicity will be needed in the future.

Individualized and Targeted Therapy

In Vitro: Chemosensitivity Testing

Chemosensitivity testing is an ex vivo way to determine the effect (endpoint can be cytotoxic-, cytostatic-, or apoptosis-inducing) of anticancer drugs on survival of cancer cells [64]. The clinical utility of chemosensitivity analysis for selecting a "personalized" HIPEC regimen is largely unknown. In 2013, the University of Uppsala demonstrated that the variability in ex vivo drug sensitivity in the CRC subgroup was large, rang-

ing from virtually no to total cell death [65]. In 2014, they showed in vitro drug sensitivity testing on samples obtained preoperatively to be clinically relevant in epithelial ovarian cancer. Furthermore, they used ex vivo drug sensitivity testing on samples obtained during CRS and HIPEC for patients with pseudomyxoma peritonei, showing a possible impact of IPC on PFS but not OS [66].

3D Culture

In vivo treatment response reflects not only properties intrinsic to the target individual malignant cells but also cell-to-cell interactions and extracellular components. For this reason, preserved 3D tumor-stroma structures from biopsy fragments may provide a more accurate model to predict treatment effect [67]. However, numerous limitations to this approach also exist: the influence of tumor resection, transport, and processing of cells for culture (either by mechanical or by enzymatic degradation) disturb the tissue, the ECM surrounding tumor cells is destroyed, and selective growth of subpopulations of cells may occur. In vitro growth rate usually is much faster than in vivo, leading to potential overestimation of chemosensitivity.

In Vivo: Tumor-Bearing Animal Models

The mouse (athymic, severe combined immunodeficient, or triple deficient) is a commonly used tumor-bearing model [64]. Human tumors can be grown subcutaneously as xenografts, and its growth can be studied by size measurements to construct growth curves and assess changes induced by treatment by various chemotherapy agents. Unfortunately, the correlation to treatment effects observed in patients has been variable, limiting the utility of this approach in clinical practice.

Molecular Basis of Chemosensitivity and Resistance

The current "one-treatment-fits-all" approach to chemotherapy treatment regimens, either systemic or locoregional, does not take any tumor nor patient-related variability into consideration which likely has a large impact on the cost-effectiveness. Studies to understand the molecular basis of drug effectiveness/resistance at the gene as well as the protein level have been crucial in the push for developing targeted therapies. It is important to point out that molecularly based drug resistance can exist at the onset of disease or be acquired after exposure to chemotherapy by developing escape mechanisms. In addition, tumors are known to be genetically dynamic, acquiring more genetic alterations as they evolve, leading to potential differences in chemosensitivity between the primary tumor and the metastases, explaining at least in part the phenomenon of heterogeneous response to treatment [68]. Two molecular approaches to studying prediction of treatment effect are currently used [69]:

Genomic Approach

Gene expression arrays have highlighted the great heterogeneity among cells with histologically similar appearance [70, 71]. Pharmacogenomics aim to accurately predict a patient's response to a drug in order to individualize treatment by focusing on genes that influence drug metabolism [72].

Cancer genomics refers to analysis of the cancer genome to identify specific genetic loci that are recurrently altered in specific cancer types. While many mutations have been shown to correlate with prognosis, a few examples of signatures that have also been predictive of outcomes with treatment exist [73].

For some drugs, chemosensitivity might be governed by mechanisms that are not readily revealed at the transcriptional level, such as posttranscriptional regulation, posttranslational

modification, proteasome function, or protein-protein interactions. In these cases, a proteomic approach could increase the predictive accuracy [72].

Proteomic Approach

In this analysis, protein markers are used for prediction of response to anticancer drugs which are more likely to reflect epigenetic influences as well as gene polymorphism. Addition of these studies (to genomic) will further facilitate the ability to a priori differentiate sensitive from resistant tumors. Simple IHC analysis of paraffin-embedded tissue can be used such as determination of MSI status in colorectal cancer and its association with response to immunotherapy.

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