Review

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Pharmacokinetic problems in peritoneal drug administration: an update after 20 years

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Abstract: Intraperitoneal chemotherapy has demonstrated significant pharmacologic and clinical advantage over traditional intravenous administration for cancers that are restricted to the peritoneal cavity. The combination of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) has become the standard technique used to fight ovarian and gastrointestinal cancers in many centers. However, challenges remain for HIPEC to contact the entire peritoneal surface, penetrate the tumor tissue, and transport to the lymphatics and other metastatic sites. New innovations in delivery technique, such as heated aerosol, and in delivery molecules, such as microparticles, nanoparticles, nanogels, and tumor-penetrating peptides are being tested in animal models and will likely soon be in human trials. Improvements in overall care, such as the recent clinical trial of an oral agent for maintenance therapy in ovarian carcinoma, will continue in this field for the next 20 years.

Keywords: contact area, cytoreductive surgery, drug penetration, hyperthermic intraperitoneal chemotherapy, tumor-penetrating nanoparticles

Introduction

Despite advances over the past 20 years in treatment options for metastatic ovarian or gastrointestinal cancers, survival is relatively poor. Ovarian cancer is the sixth most common neoplasm in women [1], and local recurrence of stomach, pancreas, colo-rectal cancers varies between 30 % and 60 % [2–6]. The chief strategy that is employed at present is a combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) [1, 6]. HIPEC is a regional treatment involving a heated solution in the peritoneal cavity and high drug concentrations [6, 7]. HIPEC is often performed immediately after peritonectomy and visceral resection to remove cancer that can be detected. Variations of this treatment such as use of a heated aerosol [8] are used before cytoreductive surgery and HIPEC. Tumor cells from the primary cancer can invade the serosa or local blood vessels or migrate to the local lymphatics that subsequently drain from the intestinal tract to cisterna chyli or directly from the peritoneal cavity to the sub-diaphragmatic lymphatics. Treatment solutions in the peritoneal cavity can penetrate not only the local tissue but also these same lymphatic routes. The presence of ascites may indicate that these lymphatics are blocked by the tumor cells. To the extent that HIPEC: (a) covers the peritoneal surface, (b) penetrates the tissue, and (c) transports the active agent to the lymphatics, the technique treats the residual cancer and prevents peritoneal metastases of the primary malignancy. These factors are the technical challenge and depend on the molecular size of the agent used, the peritoneal area in contact with the solution (volume and mixing conditions of the solution), the intraperitoneal pressure of the solution (important for penetration of larger molecular sizes), and the microenvironment of the tumor (i. e., interstitial pressure). This paper will review the state of the art and technical innovations in delivery of agents and in the agents themselves.

Theory

As discussed in our previous publication [9], the simplest model to estimate the mass transfer of a small (MW<6,000 Da), non-metabolized, water soluble drug across the peritoneum is the following:

$$\text{Rate of Mass Transfer} = PA(C_P - C_B) \quad (1)$$

where PA=the mass transfer-area coefficient (see [10, 11]) and C_P=concentration in the peritoneal cavity, C_B=concentration in the blood.

We extended that equation to the description of the free drug in the normal extracellular space (C_e) to be:

$$C_e = C_B + (C_P - C_B)\exp[-(k/D)^{1/2}X] \quad (2)$$

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where D=diffusivity of the drug in the extracellular space and k=rate constant of removal of the drug by the circulation (see reference [9]). The term "normal" typically means that blood vessels are distributed approximately evenly throughout the tissue space and extracellular tissue pressure in the range of −1 to 0 mmHg. This simple model provided estimates of the penetration (to a low point of 5% of the peritoneal concentration) of an EDTA-sized molecule at approximately 400–500 μm in the gastrointestinal tract of the rat [12]. This is perhaps the most significant reason for cytoreductive surgery: theoretically, penetration of a small agent can be less than 1 mm.

However, there are a variety of factors that will alter this estimate [13]. An irregularly distributed vasculature of a tumor can affect the properties of the interstitium or microenvironment and can alter the diffusive transport of a small molecule. The drug will likely be taken up by tumor cells and metabolized, and the concentration could drop off rapidly and be difficult to estimate [14]. The total drug taken up by a tumor for could be significantly enhanced over time: Los et al. [15, 16] measured the platinum distribution in CC531 colon adenocarcinoma implanted in the rat peritoneum and determined that concentrations were significantly elevated at 1 mm from the peritoneum after 24–48 h. Others have shown that the penetration depth for most alkylating agents is on the order of 1–3 mm [17].

Au et al. [18] has developed a sophisticated multiscale tumor, spatiokinetic model for intraperitoneal therapy, which assumes contact of the treating solution with the tumor surface. This effort models paclitaxel, both free and drug bound to soluble proteins, the transfer from the cavity via lymphatic drainage, transperitoneal transport, and subperitoneal tumors and tissue, as well as the disposition in the systemic compartment with final elimination. The tumor is modeled with a variable cell density, and transcellular and transvascular transport are included within the interstitium. Model output is fitted to in vivo data of 6 h ^{3}H-paclitaxel autoradiography with densitometric standards. A subsequent sensitivity analysis demonstrated that parameters such as tumor interstitial diffusivity, vessel surface area per unit tissue volume, and maximum cellular binding capacity were the most important to model output. This model predicts penetration of the agent given that the agent is in contact with the tumor for a specified amount of time. Others have made efforts to model or measure the penetration of macromolecules into tumors [19–22].

Area of contact

Of paramount importance to intraperitoneal therapy is the area of contact of the chemotherapeutic solution with all potential targets. Sugarbaker [23] infused blue dye into the peritoneal cavity and demonstrated that intraperitoneal fluid distribution and contact with the peritoneum was quite variable, likely due to post-operative adhesions and folds of the peritoneum in contact with each other. To correct for this, a technique of expansion is used to reach as many surfaces; Sugarbaker [24] introduced the "coliseum technique" that involved attaching the skin of the abdomen to a retractor ring that was suspended above the laparotomy wound. A plastic sheet covered the wound to allow the surgeon's hand to stir the solution in the cavity in order to achieve a more uniform exposure of the solution throughout the cavity. Others developed a "peritoneal access device" to achieve maximum exposure of the solution to the peritoneal surface [25, 26]. While both of these techniques help to distribute the fluid throughout the cavity, the loss of heat from the open wound resulted in decreased hyperthermia effects and creation of a toxic aerosol in the operating theater. There were also portions of the parietal peritoneum that were not fully exposed and this could possibly create a site for tumor reoccurrence [27]. To remedy this, a closed system is used with a single inflow catheter and one or more outflow catheters [28, 29]. While the closed system allows better control of the heat and perfusion, it may re-introduce tumor cells back into the cavity [29] and decrease access of the solution to all peritoneal areas, even limiting fluid contact with some stirring techniques.

In a recent paper, Lotti et al. [30] discuss laparoscopic HIPEC, which is proposed as a bridge between open and closed techniques. After cytoreductive surgery, four Jackson–Pratt drains are inserted into the abdominal cavity (right subphrenic, right inferior, below the left hemidiaphragm, left pelvis) to provide for outflow of the treatment fluid. A separate catheter is inserted into the left flank to measure the intra-abdominal pressure, along with two thermal probes. The abdominal wound is closed with multiple locking sutures with three balloon trocars at the junction of the sutures, with the upper trocar connected to the HIPEC inflow tube, the middle trocar to the heated CO_2 insufflator to establish pneumoperitoneum (intraperitoneal pressure=12 mmHg), and the lower trocar is connected to the smoke evacuator device. The upper trocar is used for inflow and laparoscopic viewing of the peritoneum. The abdominal contents are stirred by two palpators via the middle and lower trocars, with the cycle being 90 min of perfusion alternating with 5 min of

stirring and 10 min of perfusion. After the procedure, the trocars, pressure catheter, and thermal probe are removed, and the wound is reopened, as required. While complicated, the procedure is proposed to reach the entire peritoneum, including the abdominal wall.

Effect of heat

Intraperitoneal therapy can be carried out with or without heat. Spratt et al. carried out some of the earliest research into this technique in 1980 [31, 32]. This group first demonstrated the technique in dogs, and subsequently reported its use in a patient with pseudomyxoma peritonei, after extensive resection of the tumor including the ascending colon, the transverse colon, the omentum, the spleen and the distal pancreas. Two catheters were placed in the cavity: one in the upper left quadrant with the end laid into the subphrenic region, while the second was placed in the lower right quadrant with the end on the pouch of Douglas. Methotrexate and thiotepa were infused with concentrations over 30 min in the cavity being 1,000 times those observed in the serum [23].

Optimal temperatures are typically between 42 and 43 °C, where synergy exists between heat and drug toxicity [33]. Hyperthermia of >42.0 °C induces alterations in the microenvironment and tumor blood flow that impair oxygen supply and induce acidosis. These effects likely combine to decrease the nutritive blood flow to the tumor. Most alkylating agents, such as cyclophosphamide and ifosfamide, nitrosources such as carmustine and lomustine, bleomycin, nucleoside analog (gemcitabine), and the platinum compounds are enhanced in their cytotoxic properties at temperatures above 40.5 °C, while 5-fluorouracil demonstrates no increased cytotoxicity with increased temperature [34].

The range of effects of hyperthermia on the cell includes: destabilizing the cell membrane, changes in cell shape, impaired transmembrane transport, changes in membrane potential and modulation of transmembrane efflux pumps, induction of apoptosis, impairment of protein synthesis, protein denaturation, aggregation of proteins at the nuclear matrix, induction of heat-sensitive protein synthesis, inhibition of enzyme repair, altered DNA conformation, alteration of intracellular metabolism of other substrates, and alteration of gene expression and signal transduction [17, 33]. However, thermo-tolerance has been observed with different forms of drug resistance [35].

Typically, the heated solution is infused into the peritoneal cavity immediately after cytoreductive surgery and circulated or allowed to dwell 60–120 min. This is followed by early post-operative intraperitoneal chemotherapy (EPIC) is begun in the first post-operative day and the solution dwells for 23 h, drained for 1 hour and then re-administered; the duration of therapy is typically 1 week [17]. Complications due to the heated solutions are due to bowel perforations due to surgical trauma. [26, 29, 36–40]. Systemic toxicity, especially renal failure due to platinum drugs and heat, is a major consideration [37–40].

Penetration of intraperitoneally delivered agent

Tissue penetration is a major impediment to the success of intraperitoneal delivery. In normal tissue, the interstitium is −1 to 0 mmHg [41], and penetration of small molecules (MW<1,000 Da) conforms to the typical diffusion gradient [11, 42, 43], while penetration of larger molecules is dependent on intraperitoneal pressure (typically 4–10 mmHg) [44–46]. In animal models [47, 48], Flessner demonstrated that some tumors exhibit high interstitial pressures (10–20 mmHg) that set up a pressure-driven convection outward from the tumor to the periphery. This creates a convective barrier to large solutes that depend on pressure to propel the molecules to the interior of the tumor and effectively blocks penetration to these tumors with high pressures [47–50]. Human tumors as well have high interstitial pressures as noted in many studies [51–55]. Small solutes may also be retarded in their transport, depending on the tumor interstitial fluid movement from the interior to the periphery [56]. Gremonprez et al. [57] demonstrated that pretreatment of the tumors with gavage-treatments with vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) inhibitors decreases interstitial pressure (from 20 to 5 mmHg), increases penetration of oxaliplatin and slows tumor growth in a mouse colorectal cancer model.

Innovations in intraperitoneal chemotherapy

PIPAC: pressurized intraperitoneal aerosol chemotherapy

Among recent innovations in intraperitoneal drug delivery is PIPAC, the use of a novel clinical approach to

enhance penetration of the drug, enhancement of the area covered, and delivery of the dose. This technique uses a probe placed through the abdominal wall and connected to a micropump to deliver the pressurized aerosol. Reymond et al. [58] tested the feasibility of a pneumoperitoneum in a large animal model using a microvaporisator, in an effort to overcome the limitations of intraperitoneal chemotherapy including direct penetration of drugs into tumor tissue and the unequal distribution throughout the cavity. They combined gas and pressure in order to overcome these problems and noted improved coverage of the entire surface of the peritoneum over and above the typical "peritoneal washing". The group subsequently tested the concept in a box with an excised tumor section: they determined that under a pressure of 12 mmHg, penetration of the tracer material was 1 mm [59, 60].

Subsequent studies demonstrated in a Phase 2 study in women with ovarian carcinoma that the 30 min application of cisplatin and doxorubicin resulted in an objective tumor response in 76 % of the 34 patients treated with three treatments over 28–42 days with only a few serious adverse events [61–63]. Liver and renal toxicities appear to be minimal [64], and quality of life was maintained in a cohort of 91 patients [65, 66]. The most recent use of PIPEC has been as an adjuvant therapy in preparation for surgical cyto-reduction and HIPEC [8].

Jung et al. [66, 67] has tested a hyperthermic version of PIPAC in swine, which he has termed H-PAC. Surgery included placement of three trocars: one in the superior peritoneum, one just beneath the umbilicus, and one in the lower pelvis. Any of the trocars could be used for the laparoscope, and the mid-abdomen was considered the most favorable site to administer the solution as an aerosol spray. Insulating the heated CO_2 line was found to be necessary to prevent loss of heat. The temperatures of the solution delivered were 38.7–40.8 °C, and the authors considered the experiments a success, although they did not check the area covered or the depth of penetration in the experimental tissues.

A second innovation in the PIPAC technique has been offered: electrostatic precipitation as an adjunct to pressurized intraperitoneal aerosol chemotherapy, termed ePIPAC [68]. After applying PIPAC [69] by inflating the peritoneum to 12 mmHg and inserting two balloon safety trocars into the abdomen and infusing the pressurized aerosol for approximately 30 min, an electric current was added for 30 min via an electrode in the abdomen. The negatively charged particles were then deposited on the positively charged peritoneal tissue. Toluidine blue was in the solution used to determine the tissue area distribution and noncoding small DNA fragments labeled with Cy5 (DT01) were used to determine tissue penetration. Results in pigs demonstrated spread of the solution to many parts of the peritoneum and somewhat better penetration with ePIPAC than standard PIPAC ($p<0.06$); there was almost no DT01 left in the peritoneal cavity after ePIPAC vs. PIPAC ($p<0.01$).

However, in a simulated ex vivo delivery at a pressure of 12 mmHg, Khosrawipour et al. demonstrated that the position of the tissue directly under the spray nozzle had a major impact on the concentration delivered to the tissue [70]. Penetration was significantly affected by drug (doxorubicin) dose but not by pressure [71]. Irradiation of the tissue prior to treatment did not enhance the penetration [72]. In a postmortem swine model [73], doxorubicin was aerosolized into the peritoneal cavity at a pressure of 12 mmHg and 32 °C, and the distribution and depth of penetration were determined a nine different positions in the cavity. These experiments demonstrated a variable penetration in all tissues, with the highest concentrations in the tissue closest to the pump probe.

Innovative agents for intraperitoneal chemotherapy

Lu et al. [13] have outlined optimal characteristics for the development of drug-loaded tumor penetrating microparticles:

- Have long retention in the peritoneal cavity;
- Selectively adhere to tumors;
- Have deep tumor penetration;
- Provide instantaneous and sustained drug release to obtain optimal peritoneal delivery.

Absorption is a passive process of diffusion and convection (with the proviso that the delivery pressure is greater than the tumor interstitial pressure). Molecules that are less than 20 kDa can easily cross the peritoneum [74], but larger substances (molecular size=50–200 nm) transport chiefly via the lymphatics and may be taken up by the lymph nodes [75]. Therefore, free drugs or nanoparticles that <50 nm are capable of absorption into the surrounding tissue. Smaller particles (<5 μm) distribute widely in the peritoneal cavity [13], while larger particles may collect in the lower part of the abdominal cavity [76]. Selective adherence of the microparticle is desirable; activated carbon particles have shown promise with certain sarcomas [77]. Tumor priming, such as use of a drug such as paclitaxel or doxorubicin to

expand the tumor interstitial space [78–80] is useful in enhancing drug transport and drug penetration.

Preclinical agents

The determination of platinum in tumor tissue has been recently improved by Carlier et al. [81]. This group used a synchrotron radiation X-ray fluorescence spectrometry and laser ablation-inductively coupled plasma-mass spectrometry to measure platinum distribution and penetration in ovarian cancer peritoneal xenografts after intraperitoneal administration of cisplatin at two different temperatures. Using principal component analysis, they correlated several molecules with the distribution of platinum. The results demonstrated higher concentrations of platinum after hyperthermic perfusion and increased penetration. However there were no differences in platinum distribution between cells and stroma.

Tsai et al. [82] exposed mice to intraperitoneal paclitaxel in 3 formulations: Cremophor formulation, paclitaxel-loaded gelatin nanoparticles, and polymeric microparticles to evaluate their advantage in targeting and treatment of tumors. They utilized whole-body, quantitative autoradiography to determine the relative distribution in tissues and penetration, and found slower drug clearance with the microparticles, 5–22 times greater advantage, and twice the survival advantage. They [83] subsequently investigated the effects of smaller (dia=5–6 μm) vs. larger (50–60 μm) microparticles in a murine model of pancreatic cancer and found that the smaller particles were more evenly distributed in the peritoneal cavity and demonstrated longer survival and higher dose efficiency. Au et al. [84] has recently reviewed these preclinical results as a preliminary step in the use of drug-carrying microparticles in an investigational new drug (IND)-enabled study.

Paclitaxel can also be combined with mesoporous silica nanoparticles to treat ovarian carcinoma [85]. Subsequently, Fu et al. extended the results and used in vivo imaging in a murine model at three different times and then sacrificed and cryo-sectioned the animals to study the penetration of the nanoparticles [86]. This group used tumor bearing mice to compare IV with intraperitoneal administration of paclitaxel. Marked increase in cellular accumulation of paclitaxel occurred with silica nanoparticles vs drug alone.

Cisplatin-incorporating hyaluronan (HA) nanogels have recently been fabricated by mixing the drug with conjugating chelating ligands (iminodiacetic acid or malonic acid to HA) to form a cross-linked, cisplatin-loaded hyaluronan nanogels [87]. The HA gels selectively inhibited the growth of gastric cancer cells. In vivo experiments in a murine model demonstrated the HA nanogels specifically localized to the peritoneal nodules after intraperitoneal administration. Penetration assays showed a significantly higher ability to penetrate tumors than unconjugated hyaluronan.

Tumor-penetrating peptides are a class of new tools in treating metastatic peritoneal carcinoma that transport actively through tumor tissue [88]. These substances require a primary receptor, proteases, and neurophilins. These peptides bind to a tumor-specific receptor (e. g., integrins) and are then converted to bind neurophilin-1 or neurophilin-2′ this exposes a c-terminal amino acid sequence for the neurophilin (NRP) binding [89]. One such tumor-penetrating peptide, a 9-amino-acid-based cyclic, arginine-glycine-aspartic acid (RGD) has the necessary characteristics to enhance penetration of co-applied molecules into peritoneal tumors, no matter the degree of vascularity and improves the therapeutic index. Sugahara et al. [90, 91] demonstrated these properties with a murine model of disseminated gastric cancer with imaging and immunostaining of the harvested tissues. The animals were also co-injected with dextran and/or doxorubicin and demonstrated marked differences in those animals with the iRGD molecule with increased penetration (3–10 mm vs 0.5 mm) over the non-tumor penetrating peptide. iRGD also facilitated entry of dextran into both avascular and vascularized peritoneal tumors with intraperitoneal-coinjection. Other non-penetrating peptides did not facilitate dextran entry. In preparation for human studies, they showed similar properties in excised human tumors [92]. This group has demonstrated facilitation of tumor penetration with iRGD conjugated to polymerase in the treatment of colon or gastric cancer induced in murine models [93, 94].

Clinical innovations

Recurrent ovarian cancer is a serious problem that continues to challenge clinical researchers. Fagotti et al. obtained encouraging results in two Phase 2 studies on the use of HIPEC following secondary cytoreduction in patients with recurrent platinum-sensitive ovarian cancer [95, 96]. They subsequently carried out a case-control study in patients who had platinum-sensitive ovarian carcinoma with 30 cases and 37 controls and 24 months of follow-up [97]. They found that survival was significantly better at 2 years (96.7 vs 75.7 %) and at 5 years (68.4 vs. 42.7 %) with HIPEC (with the administration of oxaliplatin 460 mg/m^2 at 41.5 °C) than with chemotherapy or surgery plus chemotherapy. This group [98, 99] screened 231 women between 2004 and 2015 with platinum-sensitive ovarian cancer. Approximately 83 % of the women had stage 3 or 4 disease as well as serous

(85%) and high-grade (93%) ovarian cancer. Nearly all underwent primary debulking. The screening process reduced the population to 70 for recurrent disease with all undergoing secondary cytoreduction plus HIPEC with either cisplatin (38.6%) or oxaliplatin (61.4%); follow-up time ranged between 48 and 128 months with 34 deaths and 36 who survived. These findings demonstrate the effectiveness of HIPEC in platinum-sensitive ovarian cancer.

As detailed above, there is significant research in the use of nanoparticles as means of drug delivery to peritoneal malignancies. In a recent Phase 1 study, Williamson et al. [100] detailed findings of an open-label, dose-escalating examination of the safety, tolerability, pharmacokinetics and preliminary tumor response of Nanotax, a nanoparticulate formulation of paclitaxel. The particles had a diameter of 600–700 nm, with 95% of all particles measuring less than 1 μm [101] and provided a stable reservoir of paclitaxel allowing for extended drug release. This was administered intraperitoneally in patients with solid tumors confined chiefly to the peritoneal cavity. All 21 patients had undergone chemotherapy and surgical procedures. Six doses of cremophor-free Nanotax (50–275 mg/m^2) were administered in 2–2.5 L solutions for 30–60 min in one to six cycles, every 28 days. There were minimal side effects with regard to neutropenia or neurologic toxicities. One patient had thrombocytopenia that was unlikely related to Nanotax. The peritoneal concentrations were 450–2,900 times greater than the peak plasma concentrations and remained elevated through the entire dose cycle. Four patients were stable while 12 had increasing disease. Five patients survived greater than 400 days after initiation of the Nanotax treatment.

Mirza et al. [102] have just published the results of a double-blind phase 3 trial of Niraparib, an oral poly(adenosine diphosphate [ADP]-ribose) polymerase 1/2 inhibitor that has clinical activity in patients with ovarian cancer and which was proposed as maintenance therapy. In the cohort of 553 patients, there were both gBRCA and non-gBRCA cohorts that were assigned either Niraparib or placebo. Patients in the Niraparib group had a significantly longer median duration of progression-free survival (21 vs. 5.5 months in the gBRCA cohort and 9.3 vs. 3.9 months in the non-gBRCA cohort). Bone marrow toxicity resulted in 34% thrombocytopenia, 25% anemia and 20% neutropenia, which were managed with dose modifications.

Conclusions

Significant progress in the treatment of peritoneal malignancies has been made over the last 20 years. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy has increased survival and extended lives. New agents and techniques of intraperitoneal therapy have been designed to insure coverage of the entire target area, penetration of the target tissue and in some cases targeting of the tumor with the goal of increasing survival times. However, most of these developments need more widespread clinical testing, and therefore, challenges still remain for researchers, oncologists, surgeons, and patients.

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