6 Historical Perspective for Regional Peritoneal Therapy: HIPEC, EPIC, and Port-Based Therapy

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Introduction

From the beginning of the clinical and pharmacologic exploration of the utility of chemotherapy administration into the peritoneal space, the prospect for profound dose intensity was recognized. Dedrick and Flessner showed that the exposure of peritoneal surface cancer nodules could be increased logarithmically by chemotherapy instillation directly into the peritoneal space as compared to intravenous drug delivery [1]. Drugs with a large molecular weight will remain in the peritoneal space for a prolonged time period causing the ratio of intraperitoneal drug concentration times time to be much greater than the plasma drug concentration times time. This area under the curve (AUC) ratio of intraperitoneal to intravenous exposure of peritoneal surfaces has long been used to select agents for intraperitoneal administration. Speyer and colleagues demonstrated the marked differences in the activity of 5-fluorouracil when the drug is delivered by continuous infusion, by bolus intravenous injection [2], or by intraperitoneal administration. The metabolism of drug within the body compartment is always more rapid than its clearance from the peritoneal space. This causes large differences in intraperitoneal as compared to intravenous drug concentration over long time periods. This phenomenon is demonstrated in Fig. 6.1.

Dose Intensity of Chemotherapy for Peritoneal Metastases by Intraperitoneal Administration

Sugarbaker and colleagues tabulated the chemotherapy agents that may be used for intraperitoneal instillation. A maximal AUC ratio was shown to be approximately 1000 for paclitaxel and pegylated liposomal doxorubicin. Several drugs show an AUC ratio between 100 and 200 including doxorubicin, 5-fluorouracil, gemcitabine, and mitoxantrone. Pertioneal exposure with AUC ratio under 100 occurs with floxuridine, melphalan, and pemetrexed. Mitomycin, often used for intraperitoneal administration, has an AUC ratio of 27. Some drugs leave the peritoneal space in 20 minutes or less. These drugs include carboplatin, cisplatin, and oxaliplatin. Clearly, the dose intensity of intraperitoneal drug administration will depend greatly on the choice of chemotherapy agent [3].

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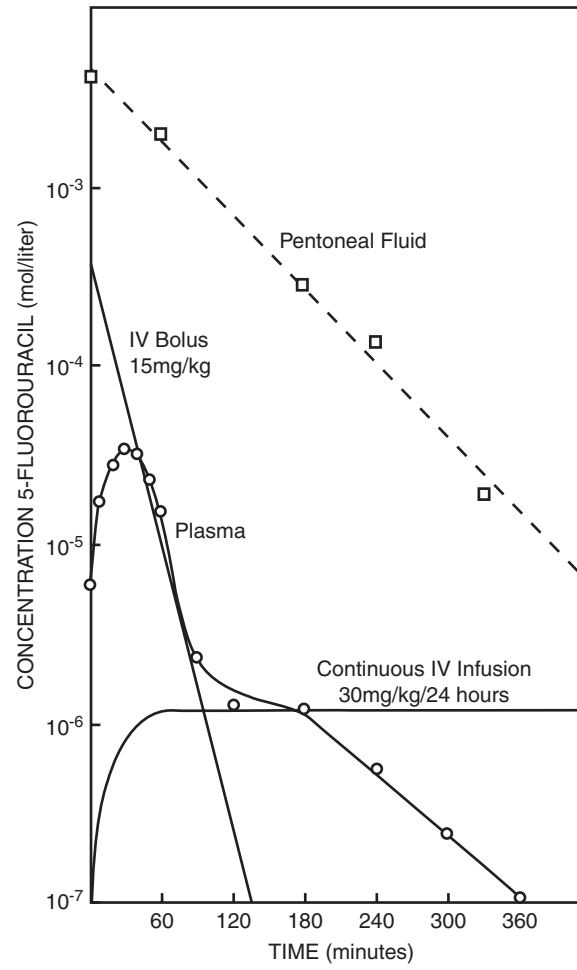

Fig. 6.1 Diagram of three methods of 5-fluorouracil delivery. □ peritoneal fluid, ○ plasma. (From Speyer et al. [2]; used with permission)

Limited Intraperitoneal Drug Penetration into Abdominal and Pelvic Tissues

Chemotherapy agents that are administered via the intravenous route are rapidly distributed to all tissues of the body exclusive of the brain and spinal cord as a result of the "blood–brain barrier." In sharp contrast, drugs instilled directly into the peritoneal space have very limited access to the tissues within the abdomen and pelvis. Drug penetration is by simple diffusion only. The rate of diffusion into tissues is largely dependent upon the concentration of the intraperitoneal drug [4]. Ozols and colleagues studied the drug penetration of the peritoneal surface by doxorubicin. They estimated 6–8 cell layers were exposed to increased concentrations of the intraperitoneal drug [5]. Los and colleagues studied intraperitoneal cisplatin and carboplatin. The cisplatin penetrated significantly better than carboplatin. The distance of the penetration was measured in micromillimeters [6].

Not only is the drug penetration limited by diffusion, the drug that reaches the rich subperitoneal lymphatic and capillary network is rapidly removed into the body compartment. Chemotherapy that does enter the tissues is rapidly distributed by the rich vascular and lymphatic network that underlies the peritoneum. As a result of these observations, the early clinical studies with intraperitoneal chemotherapy involved the prevention of peritoneal metastases.

Sugarbaker and coworkers explored this in patients with colorectal cancer [7]. Koga and colleagues explored the prevention of peritoneal metastases from gastric cancer [8].

Advantages and Disadvantages of Hyperthermic Intraperitoneal Chemotherapy Administration

There is no doubt that the inventor of HIPEC is John Spratt [9]. In 1990, at the University of Louisville, he treated a single patient with hyperthermic intraperitoneal thiotepa and repeated the treatment with hyperthermic intraperitoneal methotrexate. He called his HIPEC machine the "thermal infusion filtration system." He credited Robert Dedrick with the pharmacologic rationale for his treatments. Shiu and Fortner had previously published on the benefits of intraperitoneal hyperthermic perfusion in a rat model [10]. The invention was not appreciated in the USA, but Koga at Tottori University in Yonago, Japan, went to work in the laboratory confirming the concept of combined hyperthermia and intraperitoneal chemotherapy [11]. In 1984, he published laboratory work showing that optimal control of peritoneal metastases was achieved not by heat alone, not by mitomycin C alone, but by a combination of hyperthermia and mitomycin C chemotherapy. Fujimoto in Chiba, Japan [12] and Yonemura in Kanazawa [13] were two other Japanese investigators publishing their results of this new treatment option for prevention of gastric cancer peritoneal metastases and treatment of established disease.

The global application of HIPEC in patients with peritoneal metastases of a wide variety of primary sites has occurred within the last decade. The combination of intraperitoneal cancer chemotherapy with heat has a strong rationale in that the cytotoxicity of the cancer chemotherapy is increased by heat, the drug penetration into tissues is increased by heat, and prolonged moderate heat that can be tolerated within this peritoneal space can, in and of itself, destroy tumor nodules [14].

HIPEC has most successfully evolved for its use in the operating theater. It is employed after a maximal surgical removal of peritoneal metastases has occurred. The large benefits in terms of improved survival with cytoreductive surgery and HIPEC occur only in those patients who have complete visible removal of cancer cells on peritoneal surfaces. Also, the problem with drug distribution is eliminated through HIPEC. Surgical separation of all of the peritoneal surfaces that may be held together by scar tissue takes place prior to HIPEC being initiated. Uniform distribution of the heat and chemotherapy solution is possible with this intraoperative application of intracavitary chemotherapy.

These treatments occur in the operating room and the time devoted to the HIPEC procedures is limited. The heated chemotherapy dwell time within the peritoneal space varies between 30 minutes and 3 hours [3]. The time devoted to HIPEC will depend on the rate at which the chemotherapy is cleared from the peritoneal space. Only those chemotherapy agents which are active over a short time period should be utilized. Appropriate drugs for HIPEC are doxorubicin, melphalan, mitomycin C, cisplatin, and oxaliplatin. Drugs that require metabolism for their activity, such as 5-fluorouracil and paclitaxel, would not be appropriate for short-term peritoneal exposure [3]. Of course, another requirement for drugs used for HIPEC would be their augmentation by heat. Doxorubicin, melphalan, mitomycin C, and cisplatin are all heat-augmented.

A disadvantage of HIPEC is the requirement for a heat pump in the operating room to recirculate the chemotherapy solution. The expense, expertise, and unavailability of the apparatus limit the use of HIPEC to centers devoted to the management of peritoneal metastases.

Advantages and Disadvantages of Early Postoperative Intraperitoneal Chemotherapy

The first reported series of patients treated by EPIC was in 1995. Sugarbaker and Jablonski treated 51 colorectal and 130 appendiceal cancer patients with peritoneal metastases [15]. Their treatments were mitomycin C used on the first postoperative day and then 5-fluorouracil used on

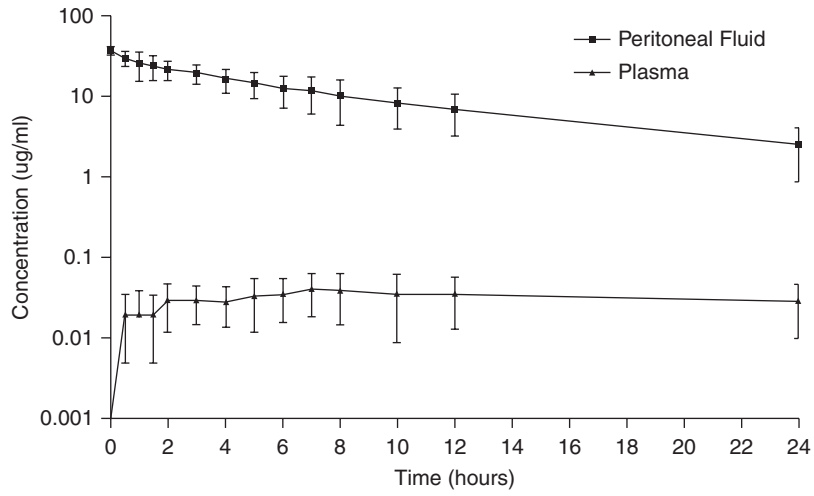

Fig. 6.2 Plasma and peritoneal fluid concentration versus time following a single early postoperative intraperitoneal administration of paclitaxel (20 mg/m^2) in eight patients. (From Mohamed and Sugarbaker [19]; used with permission)

postoperative days 2–6. The EPIC, when combined with complete cytoreduction, showed that appendiceal malignancy always did better than colorectal cancer. The histopathology was important in determining prognosis as was the completeness of cytoreduction, lymph node-positive versus lymph node-negative patients, and the volume of peritoneal metastases as measured by the peritoneal cancer index [16]. When the peritoneal metastases treatments were started at the Institut Gustave Roussy by Elias, EPIC was used [17]. To this day, EPIC is used at the peritoneal metastases unit in Basingstoke, UK [18].

Early postoperative intraperitoneal chemotherapy is instilled into the peritoneal space, either immediately after the completion of a surgical procedure or in the first 1–5 postoperative days. EPIC has the advantage over HIPEC in that is does not require a heat pump for administration. Also, EPIC can utilize those drugs which require metabolism for their activity. This involves paclitaxel and 5-fluorouracil and floxuridine. All three of these drugs are large molecules with a high AUC ratio. A third drug currently being developed for EPIC is pegylated liposomal doxorubicin (Doxil). If the cancer causing peritoneal metastases has responses to paclitaxel, this may be an ideal drug for instillation in the early postoperative period. The AUC of paclitaxel is 1000 or more. Its dwell time within the peritoneal cavity is up to 24 hours (Fig. 6.2). Also, its penetration into peritoneal surfaces may be greater than other chemotherapy agents. Paclitaxel has been used for EPIC in ovarian cancer and in gastric cancer [19, 20]. Of recent interest is the use of intraperitoneal nanoparticles. Because of the large size of this chemotherapy preparation, it has a prolonged dwell time within the peritoneal space. Very similar and sometimes even more prolonged than paclitaxel. Figure 6.3 shows the concentrations over time with a 24-hour dwell of this drug instilled in the operating room after the closure of the abdomen. It is instilled in 2 liters of fluid as the patient is being taken to the surgical intensive care unit following the cytoreductive surgery. The drug has activity for approximately 24 hours. Somewhere between 70–90% of the drug is utilized and stored in the peritoneal surfaces over the 24 hours.

EPIC has been suggested to be associated with a greater incidence of adverse events if it is applied along with HIPEC after cytoreductive surgery. Perhaps, this was true in the early experience with HIPEC and EPIC reported in the multi-institutional study by Glehen [21]. More recently, EPIC using 5-fluorouracil for gastrointestinal cancer, especially primary colorectal cancer, can create a FOLFOX-type perioperative chemotherapy regimen. In the operating room, the high-dose oxaliplatin by HIPEC is used with 5-fluorouracil administered intravenously (Elias regimen). This is followed by 2 days of intraperitoneal 5-fluorouracil (by EPIC) to maximize the effects of the periopera-

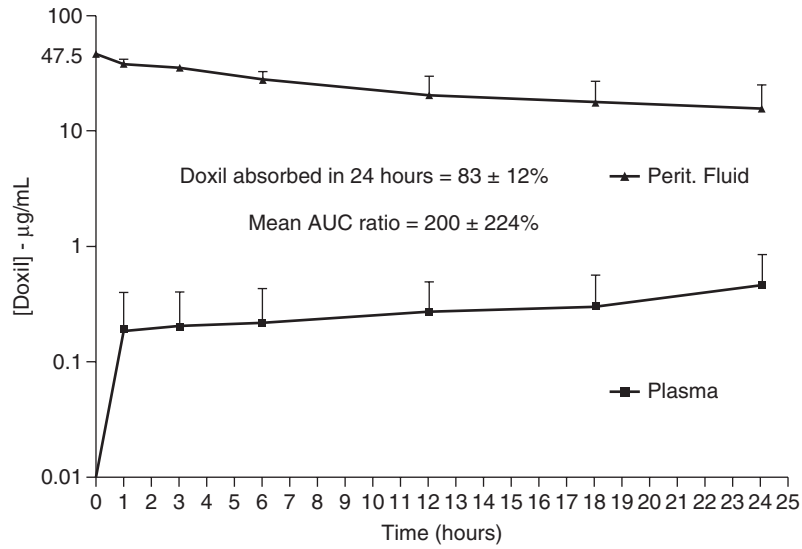

Fig. 6.3 Twenty-four hour dwell of pegylated liposomal doxorubicin. A majority of drug has entered abdominal and pelvic tissues

tive treatments. A single dose of intravenous 5-fluorouracil with the heated oxaliplatin is insufficient 5-fluorouracil dose for maximal augmentation of the oxaliplatin activity.

Advantages and Disadvantages of Normothermic Intraperitoneal Chemotherapy Administered Through an Intraperitoneal Port

The original studies with NIPEC were conducted at the Surgery Branch, National Institutes of Health. Sugarbaker and colleagues performed a randomized controlled study which compared intravenous 5-fluorouracil versus intraperitoneal 5-fluorouracil as an adjuvant treatment for poor prognosis colon or rectal cancer patients who had had a successful resection of their primary disease. Although survival in the two groups was not statistically significant, the incidence of peritoneal metastases in the two groups was markedly different with 10 of 11 intravenous 5-fluorouracil patients having peritoneal seeding and 2 of 10 of the intraperitoneal treated patients developing peritoneal seeding. These data were gathered at the time of second-look surgery [22].

The other important NIPEC studies involved ovarian cancer. The groundbreaking work of Alberts, who compared intravenous to intraperitoneal cisplatin in ovarian cancer patients must be mentioned [23]. Also, Markman and Armstrong showed positive results with intraperitoneal chemotherapy within a randomized controlled trial [24, 25]. More recently, Sugarbaker and colleagues showed that NIPEC pemetrexed gave superior long-term survival as compared to historical controls treated with intravenous pemetrexed in patients with malignant peritoneal mesothelioma [26].

The major disadvantage and lack of efficacy of HIPEC and EPIC may be the inability to administer repeated doses of cancer chemotherapy. A single large dose of chemotherapy may help control the malignant process on peritoneal surfaces but its eradication by a single treatment would require an extremely small cancer target, perhaps only single cells. A great advantage of port-based therapy is the possibility for repeated doses of the cancer chemotherapy. Also, the intraperitoneal drug can be combined with intravenous chemotherapy as a "bidirectional" treatment plan. Chemotherapy regimens that combine two drugs can definitely be simultaneously administered by intravenous and intraperitoneal routes to achieve a maximal response. Intraperitoneal taxol and systemic cisplatin may be recommended for the management of peritoneal metastases from ovarian cancer [27]. Also, intraperitoneal pemetrexed and systemic

cisplatin have been suggested to be of benefit for malignant peritoneal mesothelioma. The data from randomized controlled trials in ovarian cancer strongly recommend intraperitoneal chemotherapy using taxol as an optimal management plan for optimally cytoreduced ovarian cancer [25].

NIPEC through an intraperitoneal port does have some logistical and technological disadvantages. Perhaps, the best way to install the port is at the time of a cytoreductive surgery. If not placed in the operating room it can be implanted by an interventional radiologist with great safety. Some have proposed port placement with a laparoscopy. However, many of the patients requiring NIPEC have had extensive prior surgery and laparoscopy may not be without adverse events. Perhaps, the most important aspect of port therapy is the selection of a chemotherapy agent which does not have sclerotic effects within the peritoneal space. Drugs such as doxorubicin and mitomycin C that cause fibrosis should not be used for repeated intraperitoneal instillation through a port. However, it does not mean that these drugs cannot be used for a single intraperitoneal instillation such as for HIPEC or EPIC. Drugs that would be strongly recommended for NIPEC involve 5-fluorouracil, pemetrexed, paclitaxel, or docetaxel. These drugs have no sclerotic effects and show high AUC ratio within the peritoneal space. Also, these drugs ideal for prolonged intraperitoneal drug treatments may have systemic chemotherapy agents that will markedly augment the control of peritoneal metastatic disease. A recent randomized trial using NIPEC 5-fluorouracil for peritoneal metastases for colon cancer should be mentioned [28].

Effective management of peritoneal metastases is a new and challenging part of oncology. It requires the combined efforts of surgeon to remove all visible evidence of the peritoneal metastases and the medical oncologist to supervise the combined intraperitoneal and systemic chemotherapy that may eradicate this component of cancer progression. The profound dose intensity which is possible with intraperitoneal treatment suggests large benefit from this route of chemotherapy administration. The limited penetration of intraperitoneal chemotherapy into tissues demands careful selection of patients for treatment who have small volume of peritoneal surface disease. There are advantages and disadvantages of HIPEC, EPIC, and NIPEC. These treatment modalities should not be regarded competitive in their use for control of peritoneal metastases but should be considered complimentary. HIPEC can be used with EPIC in the same patient following adequate cytoreduction. An intraperitoneal port can be placed after the completion of the cytoreductive surgery preparing the patient for NIPEC long-term. Technical and logistical problems with all three of these potential treatments continue to exist but are, with the passage of time and with increasing experience, becoming less problematic. The proper selection of chemotherapy agents appropriate for HIPEC, EPIC, and NIPEC is an important part of their potential benefit.

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