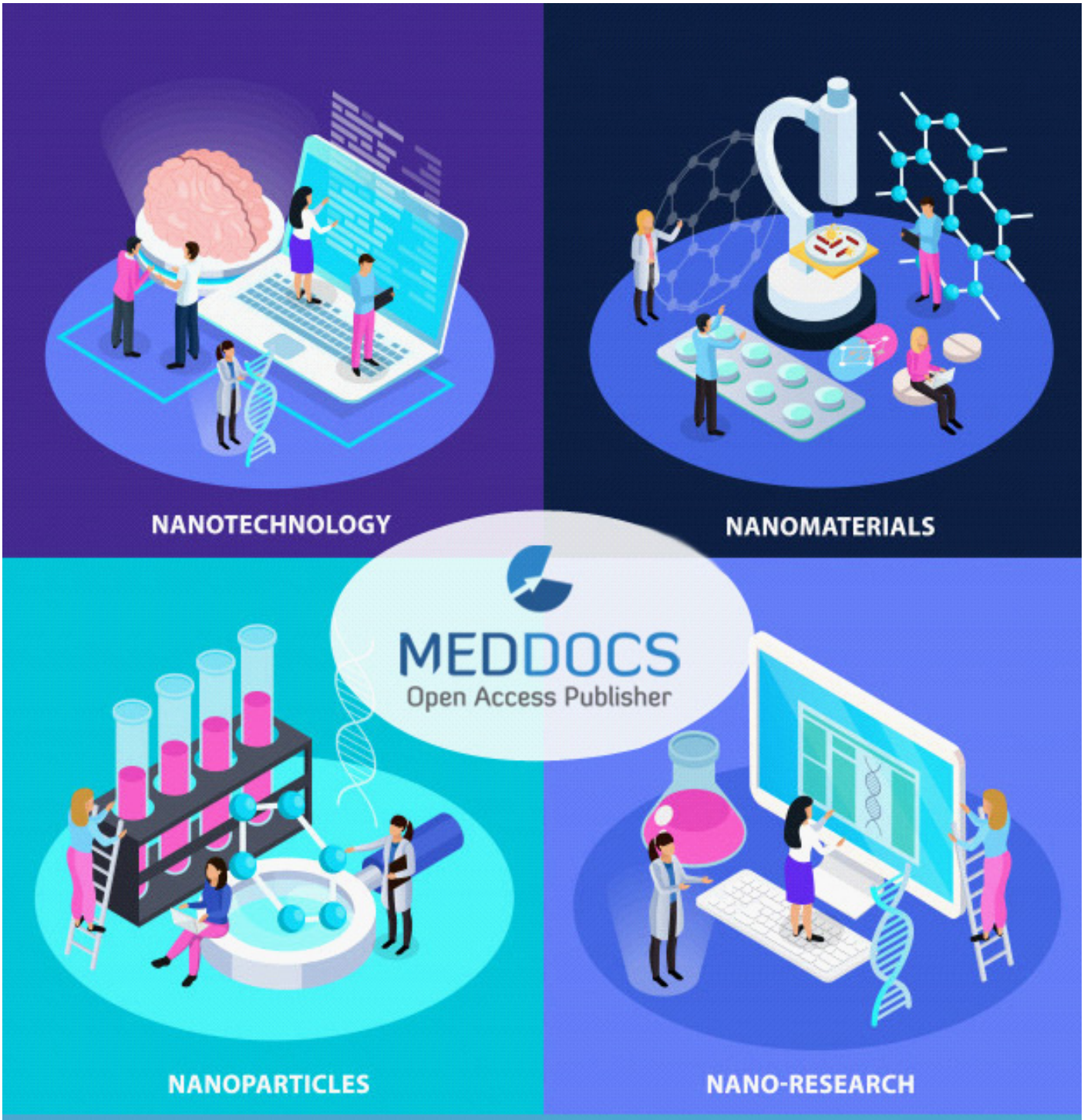

IMPORTANCE & APPLICATIONS OF NANOTECHNOLOGY

Intraperitoneal Delivery of Cancer Chemotherapy Using Nanotechnology: Rationale, Pharmacology and Early Results in Humans

Corresponding Author: Paul H Sugarbaker
Washington Cancer Institute, Program in Peritoneal Surface Malignancy Washington, DC, USA.
Tel: +1-202-844-6061, Fax: +1-202-844-2552
Email: Paul.Sugarbaker@outlook.com

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Abstract

Background: Peritoneal metastases are a major cause of death of patients with gastrointestinal and gynecologic malignancy. To improve the outcome of these patients, the intraperitoneal administration of cancer chemotherapy has been utilized.

Methods: One method for the delivery of intraperitoneal chemotherapy is Heated Intraperitoneal Chemotherapy (HIPEC). It has limited effectiveness because only a single treatment is possible, there is limited drug penetration into peritoneal surfaces, and the drug that does gain access to tissue is rapidly removed by capillary blood flow and lymph drainage.

Results: The nanoparticle, Pegylated Liposomal Doxorubicin (PLD), has pharmacologic properties that will combat all three deficiencies of intraperitoneal delivery of chemotherapy in an aqueous solution. By repeated intraperitoneal instillation through a peritoneal access catheter, multiple treatments are possible. The nanoparticle enters peritoneal tissues over 24 hours and maintains residence until degradation allows doxorubicin release. The nanoparticle is not taken up by capillaries or lymphatics so has a prolonged residence in peritoneal and preperitoneal tissues.

Conclusions: Instillations of PLD into the peritoneal space along with systemic chemotherapy may improve the control of peritoneal metastases. Further trials are indicated.

Introduction

A major problem in the cure of gastrointestinal and gynecologic malignancy is the occurrence of peritoneal metastases. Either prior to or at the time of the cancer resection, malignant cells are dispersed within the peritoneal space and over time implant and grow as peritoneal metastases. If this progression is allowed to continue, it will take the life of the patient in that there is a loss of gastrointestinal function. In order to eradicate intracoelomic cancer progression, intraperitoneal chemotherapy has been added to the surgical procedure used to resect the primary cancer. In this regard, some success in gastrointestinal malignancy has been achieved [1]. Also, in ovarian cancer, favorable results of surgery plus perioperative chemotherapy has been reported as a systematic review and meta-analysis [2]. Although moderate success has been achieved with the intraperitoneal chemotherapy delivered into the peritoneal spaces in a large volume aqueous solution, the results have not been sufficiently obvious to bring about a change in practice. This lack of profound effect of perioperative chemotherapy has three major shortcomings. First, the perioperative intraperitoneal treatments are used only once at the time of the cancer resection. A single cycle of cancer chemotherapy is unlikely to bring about a major response of peritoneal metastases that has become vascularized or sequestered within lymphatic organelles on the peritoneal surface. It may be of considerable help in pre-

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venting the implantation of cells at the sites of surgical trauma. This is the prevention of tumor cell entrapment [3]. The second cause for modest benefit with perioperative chemotherapy is from limited penetration of the chemotherapy into the tumor nodule. Heat has been used in order to encourage drug delivery into peritoneal metastases [4]. The third problem is a rapid removal of cancer chemotherapy from the peritoneal nodule by capillary blood flow or lymph flow. Although penetration of the peritoneal membrane by chemotherapy is delayed, as soon as the chemotherapy does cross the peritoneal barrier, it is rapidly transported into the body compartment.

In order to combat these shortcomings of intraperitoneal chemotherapy delivery within an aqueous solution, several strategies have been used to increase the "residence time" of the cancer chemotherapy within the peritoneal nodule and increase the responses [5]. An intraperitoneal drug delivery system using "nanomedicine-based intraperitoneal therapy" has been proposed [6]. Building on this rationale our own studies were directed at a single chemotherapy agent in an attempt to optimize the delivery of this drug to humans with peritoneal metastases. This manuscript reviews our results with the delivery of Pegylated Liposomal Doxorubicin (PLD) into the peritoneal space as a planned part of the surgical management of peritoneal metastases [7].

Rationale for intraperitoneal pegylated liposomal doxorubicin

As presented in the introduction, the major flaws preventing improved outcomes with intraperitoneal chemotherapy in an aqueous solution are three-fold. A single instillation at the time of surgery, poor penetration of drug into tumor, and rapid removal of chemotherapy from tumor by capillary and lymphatic networks. Intraperitoneal PLD may solve these theoretical and actual problems with the efficacy of intraperitoneal chemotherapy. First, through an intraperitoneal catheter, repeated treatments with PLD instilled in a large volume of aqueous solution into the peritoneal space is possible. The first instillation as Early Postoperative Intraperitoneal Chemotherapy (EPIC) is suggested to occur in the operating room as part of the perioperative chemotherapy. In addition, a simple Peripherally Inserted Central Catheter (PICC) line left within the peritoneal space would provide access for repeated instillations. At least four instillations should be possible on all patients. The inflammatory response to plastic will often cause catheter-related instillation and distribution problems after four monthly treatments. The PICC line can easily be replaced by distention of the abdomen with physiologic saline and additional catheter placed under ultrasound control by the interventional radiologist. Repeated instillations of nanoparticles are definitely necessary and also readily achievable [8].

The second problem is drug penetration into the cancerous tissue. The nanoparticle finds its way through the intracellular junctions of the cancerous tissue. This process is not immediate but will take place to allow close to 100% of the drug to gain access to the peritoneal and preperitoneal tissues over 24 hours [6]. This near perfect penetration of the peritoneal surfaces and peritoneal metastases should go a long way to solve the problems that limit drug access into the tumor nodule.

Regarding rapid removal of chemotherapy from the tumor nodule, the stealth pegylated liposomal complex becomes fixed within the tissues. It is not removed by capillary blood flow or lymphatic flow. The pegylated liposome is degraded over time. The exact time required for complete degradation of the nanoparticle has not been determined but it is projected to be over several days. This means long-term exposure of the peritoneal surface and peritoneal metastases to drug release as the nanoparticles are degraded.

Pegylated liposomal doxorubicin as an intraperitoneal nanoparticle

The initial use of intraperitoneal PLD must be credited to Harrison et al. at the New Jersey Medical School in Newark, New Jersey [9]. This group studied safety and efficacy of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with PLD following a maximal cytoreduction in patients with metastases limited to the abdomen and pelvis. Both gastrointestinal and gynecologic cancers were treated. Harrison selected patients who had undergone a complete cytoreductive surgery so that no visible evidence of peritoneal metastases remained. He administered the PLD at 40°C in 4 liters of 1.5% dextrose peritoneal dialysis solution. Escalating doses of PLD started at 15 mg/m^2 for 90 minutes.

As the dose escalation study progressed, his group determined that 100 mg of intraperitoneal PLD was safe. Nine patients were treated at the top dose of 100 mg/m^2. No major complications thought related to the intraperitoneal chemotherapy occurred. The lack of chemotherapy-related toxicities suggests that with a 90-minute instillation, even higher doses of PLD may be tolerated. The maximal tolerated dose of intraperitoneal PLD cannot be determined from the data that Harrison presented.

The manufacturer recommends that the maximal systemic dose of PLD is 50 mg/m^2, half the dose that was tolerated by intraperitoneal administration for 90 minutes. The pharmacologic explanation for this increased tolerance to PLD with a short-term intraperitoneal instillation will become clear from the drug utilization studies performed by Sugarbaker and Stuart [10].

When Harrison determined the overall and disease-free survival of the 21 patients who had complete cytoreduction and HIPEC PLD, the survivals were what would be expected for cytoreduction plus HIPEC with mitomycin C or cisplatin or other drugs commonly used as HIPEC. No unusually beneficial effects from single dose HIPEC PLD were demonstrated.

What was most interesting about this data originated from the pharmacokinetic studies that were performed. These investigators determined the intraperitoneal and systemic concentrations of doxorubicin with the HIPEC PLD treatment. The intraperitoneal concentrations of doxorubicin rose rapidly to approximately 32 µg/ml and stayed at this level for the full 90 minutes (Figure 1). This is very unusual for a pharmacokinetic study of other drugs used in HIPEC such as mitomycin C, cisplatin, doxorubicin and melphalan. These drugs will have extremely low concentrations within the peritoneal space after 90 minutes. Most drugs leave the peritoneal space within 60 minutes. The prolonged residence time of the nanoparticle within the peritoneal space was most unusual and most encouraging regarding efficacy.

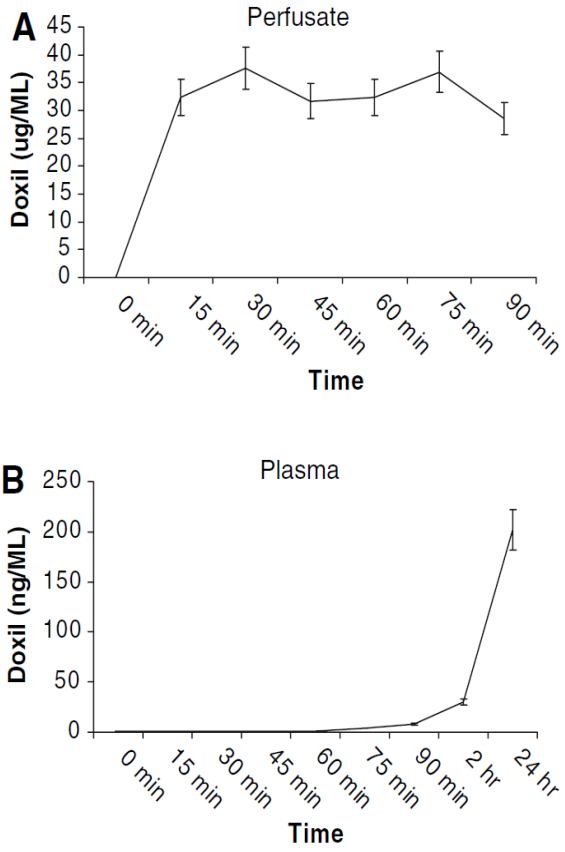

Figure 1: Time course of the mean concentrations of doxorubicin in the perfusate and plasma. Five patients underwent cytoreduction and HIPEC with PLD at the maximum tolerated dose of 100 mg/m^2. **(A)** Perfusate concentrations were measured every 15 minutes for 90 minutes are reported as micrograms of PLD per milliliter. **(B)** Serum concentrations were measured at the same time points, as well as 2 hours and 24 hours post perfusion. Concentrations are reported as nanograms PLD per milliliter. Data are reported as mean ± standard error of the mean. (From reference 9 with permission).

Also of note was the rapid rise in plasma doxorubicin over the first 24 hours after HIPEC PLD. At 24 hours post-perfusion, systemic levels reached 201 ng/ml. Only a single 24-hour specimen was taken so the concentration curve over the next several days was not determined by these studies. Nevertheless, these data suggested that there was a reservoir of PLD created at the peritoneal surface that was built up during the HIPEC. After HIPEC was complete the nanoparticles would begin to degrade causing a marked increase in serum doxorubicin levels post-perfusion. Harrison was intrigued by this unusual pharmacokinetic study of HIPEC PLD. He suggested that a phase II trial evaluating PLD at 100 mg/m^2 was indicated.

The second study of PLD in humans was carried by Salvatorelli in Rome, Italy [11]. His patient population included 17 women undergoing cytoreductive surgery for ovarian cancer. He performed HPLC assays for PLD in the intraperitoneal fluid and in the plasma. Also, specimens of normal peritoneum and ovarian cancer nodules were taken at 90 minutes to determine tissue levels of doxorubicin. Again, with drug instillation at time 0, the levels of intraperitoneal doxorubicin were relatively stable over 60 minutes. Also, plasma levels were stable over approximately 26 hours. Again, this was strong evidence that a reservoir of PLD was created within the peritoneal space that caused detection of free doxorubicin in the plasma at sustained levels for a full 24 hours. Salvatorelli and colleagues postulated that the peritoneal membrane stored the PLD within the peritoneal space. It degraded the PLD gradually over time to release free doxorubicin into the plasma over a prolonged time period.

Our studies were designed not only determine the pharmacokinetics of intraperitoneal PLD but also calculate the total drug utilization that occurred following intraperitoneal administration [10]. Our first 3 patients were treated with PLD at 50 mg/m^2. This is the recommended safe dose for systemic administration of PLD according to the manufacturer's recommendations. After 90 minutes of HIPEC using the open method with manual distribution of the heated chemotherapy solution at 41.5-43.0°C, pharmacokinetic and drug utilization studies were performed. The area under the concentration times time curve was 600. This indicated a marked increase of the exposure of cancer nodules on the peritoneal surface to the drug. At the completion of the HIPEC, the residual intraperitoneal fluid was collected and concentrations of doxorubicin determined. Our calculations showed that 73% of the PLD instilled was recovered from the peritoneal fluid after 90 minutes. In other words, at 90 minutes only one-fourth of the PLD had entered tissues within the abdomen and pelvis.

In an attempt to increase the drug utilization, patients were treated with HIPEC with PLD for 3 hours. The goal of this treatment was to increase the drug utilization through increased uptake of the PLD into the peritoneal tissues. Doses of 50 mg/m^2 and 100 mg/m^2 of PLD were used. At the higher doses of PLD, the Area Under the Curve (AUC) ratio doubled to over 1000 (Figure 2). The uptake by tissues increased somewhat going up toward 50%. However, it was clear that PLD was slowly moving from peritoneal chemotherapy solution into the peritoneal and preperitoneal tissue. With a 3-hour HIPEC (double the length of time for normal HIPEC), only about half of the drug was entering the plasma. This explains why the tolerated dose of intraperitoneal PLD is approximately twice that of intravenous PLD. The intraperitoneal instillation for 180 minutes with a removal of the chemotherapy solution following HIPEC resulted in a 50% disposal of the drug without any opportunity for chemotherapy response.

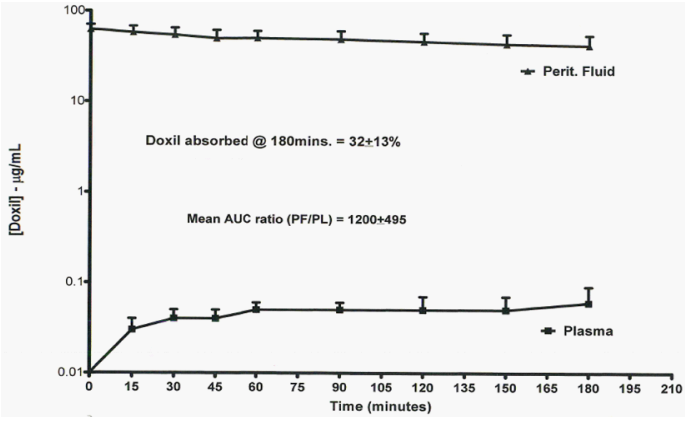

Figure 2: In order to improve drug utilization during HIPEC the duration of treatment in patients 2-7 was increased to 3 hours. The dose of pegylated liposomal doxorubicin was 50 mg/m^2 and increased to 100 mg/m^2 in 4 patients. The graph shows 4 patients treated at 100 mg/m^2. The mean AUC ratio was 1200 ± 495 and the mean percent drug utilization was 32 ± 13%. (From reference 10 with permission).

Having studied 10 patients and seeing this incomplete drug utilization, our strategy for delivering intraperitoneal PLD changed. A HIPEC with another drug, usually melphalan, cisplatin, or gemcitabine was used for intraoperative instillation. Then at the completion of the surgery and after the abdomen and vagina were closed, a catheter was positioned through the abdominal incision into the peritoneal space. A systemic dose of drug (50 mg/m^2) was instilled into the peritoneal space to remain for a full 24 hours. Drug levels were determined within the peritoneal fluid and plasma over this 24-hour time period. The percentage of PLD absorbed over 24 hours was 85±11. In other words, a majority of the chemotherapy was utilized for cancer control. When the AUC ratio was determined, it was markedly diminished from that seen with HIPEC. The AUC of peritoneal fluid to plasma was 168±193 (Figure 3).

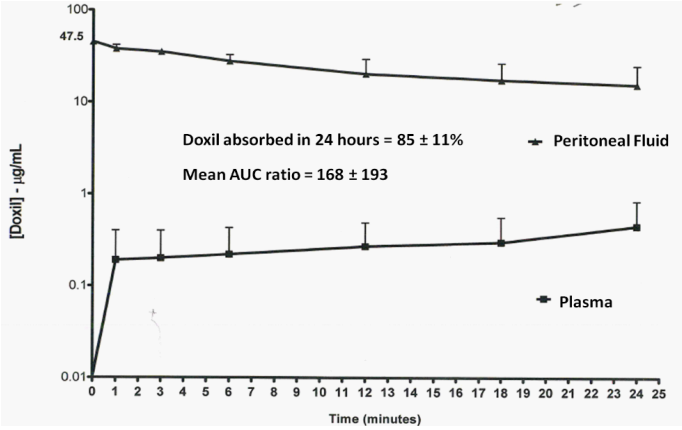

Figure 3: The pharmacokinetic graph of patients who received pegylated liposomal doxorubicin by early postoperative intraperitoneal chemotherapy with a 24-hour dwell. The mean AUC in these patients was 168 ± 193 and the mean drug absorption over 24 hours was 85 ± 11%. (From reference 10 with permission).

As a result of these pharmacokinetic studies our recommendation for the use of intraperitoneal PLD is by instillation of the drug in a large volume (2 liters) of 1.5% dextrose peritoneal dialysis solution. With this prolonged dwell time of the intraperitoneal chemotherapy nearly all of the doxorubicin left the peritoneal space and entered the peritoneal and preperitoneal tissues. Over time, the nanoparticle was degraded within the peritoneal membrane in the peritoneum and preperitoneal tissues and was released into the plasma as free doxorubicin. This instillation of intraperitoneal nanoparticle could be repeated every 3 weeks as is systemic administration of PLD. Because of the near complete absorption of doxorubicin into the body compartment the higher dose of PLD found safe by Harrison et al. would not be recommended for the instillation of Normothermic Intraperitoneal Chemotherapy (NIPEC).

In the study by Sugarbaker and Stuart, the open methodology for HIPEC was used. This allows the surgeon access to tumor nodules usually on the surface of the small bowel or small bowel mesentery throughout the 3 hours of the HIPEC. Figure 3 shows doxorubicin pharmacokinetics on a single patient treated with 100 mg/m^2 of PLD at 42°C for 3 hours. The AUC for peritoneal fluid to plasma was 882. This shows that the diffusion gradient from peritoneal fluid through the peritoneal membrane to the plasma is extremely high. Greater than in any other intraperitoneal drug except for paclitaxel [12]. What was also favorable in terms of predicting tumor response with intraperitoneal doxorubicin was an AUC ratio of tumor nodule to plasma of 33. In other words, with intraperitoneal drug instillation there was 33 times the concentration of drug within a tumor nodule as compared to the plasma. The tumor nodules were from bathed tissues submerged in the intraperitoneal PLD solution for the entire 3 hours. Also note in Figure 4 the sustained levels of PLD in peritoneal fluid, plasma and tumor nodules over the entire 3 hours. Markedly different than what would be expected from a chemotherapy agent suspended in an aqueous solution.

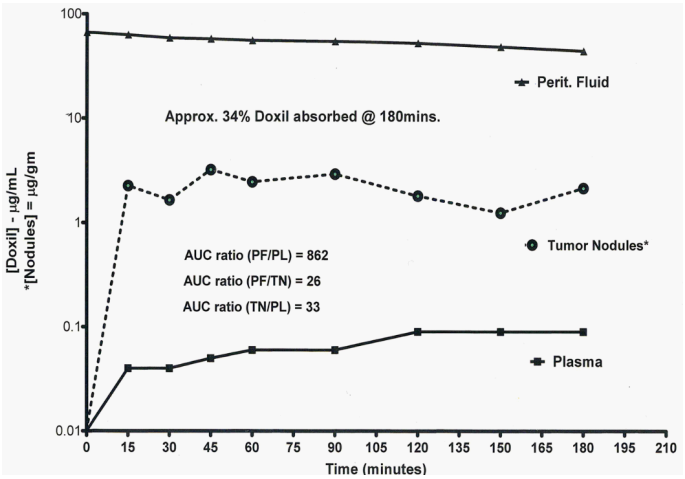

Figure 4: This 35-year-old male with mucinous adenocarcinoma of the appendix was treated with 100 mg/m^2 of pegylated liposomal doxorubicin for 180 min. The volume of chemotherapy solution was 1.5 L/m2. The graph shows concentrations of doxorubicin PLD after treatment in peritoneal fluid, tumor nodules harvested from bathed tissues, and from plasma. (From reference 10 with permission).

Concluding statements

An important step for the development of nanoparticles in the treatment of peritoneal metastases concerns the best next step for testing the efficacy of intraperitoneal PLD [13]. From our review of the literature, it can be concluded that a 24-hour instillation of at least 50 mg/m^2 of PLD in a large volume (1.5 to 2.0 liters of aqueous solution) is necessary in order to maximize the access of the drug to peritoneal tissues. In order to demonstrate efficacy, it is suggested that doxorubicin-responsive tumors should be targeted. This would include gastric cancer and endometrial cancer. Both of these diseases have a formidable recurrence rate within the peritoneal spaces following surgical treatment of the primary disease. Also, both of these diseases have important prognostic information provided by pre-resection and then post-resection peritoneal cytology. It would be wise, as these studies are initiated, to focus on cytology-positive gastric cancer patients or cytology-positive endometrial cancer patients. Of course, the surgical treatment should leave the patient with a CC 0/1 resection of disease within the peritoneal spaces. The primary endpoint for studying intraperitoneal PLD would be recurrence-free survival within the peritoneal cavity. Intraperitoneal PLD does have a local-regional dose intensity which should have in impact on the recurrence rate with peritoneal metastases. Of course, a single instillation of intraperitoneal PLD at the time of surgery would be a good place to start the treatments. However, some type of peritoneal access device, most probably a PICC catheter, would remain behind for an additional 4-6 instillations of the drug in the 4-6 months following the cytoreductive surgery. Finally, because doxorubicin in and of itself is not a sufficient treatment for either gastric cancer or endometrial cancer, the PLD instillations should occur along with the best systemic chemotherapy identified for these 2 disease processes. Some modifications of the systemic

chemotherapy protocols would be necessary. Probably a good strategy would be to use the intraperitoneal PLD between the cycles of systemic chemotherapy so that the systemic effects of the systemic chemotherapy can be separated from the systemic and possible local-regional effects of the PLD. In the best of all possible worlds, at the conclusion of the treatment a second-look surgery would be a planned part of the protocol in order to evaluate local-regional control and possible toxicity created by the repeated instillation of PLD. Although endometrial cancer and gastric cancer have been identified as a best place to start, certainly, long-term and repeated instillations of intraperitoneal PLD would be appropriate when added to systemic treatments of ovarian cancer. For example, an instillation of PLD following cytoreductive surgery with HIPEC for primary or interval resection of ovarian malignancy would be an appropriate place to start in this disease. Again, a catheter left behind for subsequent 3-6 treatments with intraperitoneal PLD would be included in the evaluation process.

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