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ORIGINAL ARTICLE

Intraperitoneal gemcitabine pharmacokinetics: a pilot and pharmacokinetic study in patients with advanced adenocarcinoma of the pancreas

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Abstract
Background The pyrimidine analogue gemcitabine (2′, 2′-difluorodeoxycitidine, dFdC) is active against pancreatic cancer, and its high clearance (CL_{tb}) and low incidence of local toxicity make it an excellent candidate for evaluation as intraperitoneal (IP) therapy. We designed a dosing schema that used multiple sequential exchanges of a peritoneal dialysate containing dFdC in an effort to produce prolonged IP dFdC exposure.
Methods As part of a study involving multi-modality therapy for advanced pancreatic adenocarcinoma, patients were treated with four 6-h IP dwells of dFdC (50 mg/m^2 in 2 l) over a 24-h period. A second 24-h cycle of IP dFdC therapy was repeated 1 week later. Each exchange of dialysate contained 50 mg/m^2 dFdC in 2 l of commercial 1.5% dextrose dialysis solution. Plasma and peritoneal fluid were analyzed by HPLC to determine concentrations of dFdC and its inactive metabolite 2′, 2′ difluorodeoxyuridine (dFdU). Clinical data were recorded to note drug toxicity and response.
Results Nine patients underwent IP dFdC therapy, and eight were able to receive two cycles. There were no recorded significant toxicities. Low plasma dFdC concentrations (<1 μg/ml) were present transiently in seven of nine patients, and dFdC was not detectable in the plasma of the other two. Plasma dFdU concentrations were low but

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increased gradually until 12 h and then declined little if any. IP dFdC concentrations declined rapidly, and dFdC was seldom measurable prior to administration of the next scheduled 6-h dwell. dFdU concentrations in peritoneal fluid were very low (<0.5 μg/ml) throughout treatment. The mean area under the concentration versus time curve (AUC) for dFdC in peritoneal fluid was 182 μg/ml × h, which was approximately 70× the AUC of dFdC reported in the ascites of a patient undergoing systemic dFdC therapy.

Conclusions IP dFdC was well tolerated, and no significant toxicities were noted. The rapid decrease in peritoneal dFdC concentrations and low concentrations of IP dFdU imply almost total absorption of IP-administered dFdC. Little, if any, dFdC could be detected in plasma, but the steady-state plasma dFdU concentrations also imply absorption and inactivation of virtually all IP-administered dFdC. These findings are consistent with the known high CL_{tb} and low incidence of local toxicity of dFdC and argue for its further evaluation as a drug for IP therapy.

Keywords Intraperitoneal chemotherapy · Pharmacokinetics · Gemcitabine · Pancreatic cancer

Introduction

Pancreatic carcinoma is the fourth leading cause of death from cancer in the United States [13]. The majority of patients with pancreatic carcinoma present with advanced disease. At diagnosis, fewer than 20% of patients have disease confined to the pancreas, and 40% already have visceral metastases [27, 34]. Although the incidence of pancreatic cancer has stabilized over the last 25 years in the United States, there has been very little improvement in death-to-incidence ratio, which continues to approach 0.95 [23].

Because the majority of patients present with locoregional disease, several modalities have been tested for disease control and/or palliation. Previous studies of combined radiation and chemotherapy for locally advanced disease indicate that while combination therapy is promising, new drugs active against pancreatic cancer need to be studied in combination with radiation therapy [7, 14, 17, 30]. The combination of neoadjuvant chemotherapy and radiotherapy also has the potential to improve outcome and is selected for better outcome after surgical resection [26].

Intraperitoneal (IP) administration of chemotherapeutic agents can be advantageous when therapeutic concentrations can be reached in the region of interest, while still avoiding local toxicity and producing non-toxic concentrations in the systemic circulation [3]. Potential limitations of IP chemotherapy include limited penetration of drug into tumor tissue and uneven distribution of the agent to the peritoneal surfaces. Some agents may also be limited by regional toxicities. Because approximately 50% of pancreatic cancer recurrences involve either the liver, lymph nodes, or the peritoneal surfaces, IP delivery of chemotherapy with subsequent absorption of the drug via retroperitoneal lymphatics and the portal circulation has the potential for controlling disease in all of those sites. Furthermore, multiple exchanges of IP chemotherapy offer the potential to maintain effective IP concentrations of the drug that is rapidly absorbed from the peritoneal cavity.

Gemcitabine (dFdC) is a fluorine-substituted cytidine nucleoside that exhibits antitumor activity against pancreatic and other cancers [31]. In contrast to the cytidine nucleoside analogue, cytosine arabinoside, dFdC has greater membrane permeability and considerably prolonged intracellular retention [10]. The experimental and clinical antitumor activity of dFdC is also much broader than that of cytosine arabinoside [15]. dFdC has single-agent antitumor activity against a variety of malignancies including lung, breast, pancreas, head and neck, and ovarian cancer [6, 12, 18, 25, 28]. When compared with 5-fluorouracil, dFdC has demonstrated an advantage in quality of life and survival of patients with advanced pancreatic adenocarcinoma [1]. dFdC requires intracellular phosphorylation by deoxycytidine kinase to produce the active species, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). dFdCTP is competitively incorporated into the cytosine sites of DNA and is associated with inhibition of DNA synthesis. dFdCDP is a ribonucleotide reductase inhibitor, which further enhances dFdCTP activity [11]. In addition to inhibiting DNA synthesis, dFdC also inhibits DNA repair. Therefore, dFdC is an attractive candidate for combination with radiation therapy [16, 19, 21, 22].

Intravenous dFdC causes short-lived myelosuppression, which is its dose-limiting toxicity, and mild transaminase increases, fever, rash, edema, and flu-like symptoms. Gastrointestinal distress, renal toxicity, and alopecia are uncommon [8].

Pestieau et al. [20] first described the pharmacokinetics of IP dFdC in a small animal model and showed peritoneal surface exposure was significantly increased with IP delivery. They also showed no significant effect of hyperthermia on the pharmacokinetic results in their model.

A previous phase I/II study to determine the dose and schedule of combination IP cisplatin and dFdC for patients with epithelial ovarian cancer showed an impressive 759-fold exposure advantage of IP over IV administration [24].

IP administration of dFdC was also reported previously by Ridwelski and colleagues, who induced carcinomatosis in rodents and subsequently instilled IP dFdC on day 0, 15, 21, or 27 [22]. All animals were euthanized after 30 days and examined for the extent of IP carcinomatosis. Perfusion

of dFdC on day 0 resulted in the largest reduction of tumor burden and showed that IP chemotherapy is capable of preventing peritoneal carcinomatosis or delaying growth [22].

Because dFdC is rapidly deaminated to the inactive metabolite 2′, 2′ difluorodeoxy uridine (dFdU), it has an exceedingly high total body clearance (CL_{tb}) [9, 29]. IP administration of dFdC should produce high IP dFdC concentrations with little systemic exposure because first-pass deamination in the liver should inactivate most of the dFdC absorbed. The primary goal of the current study was to determine the feasibility and pharmacokinetics of IP dFdC as part of a multi-modality therapy for advanced pancreatic cancer.

Patients and methods

Eligibility

Eligible patients had histologically- or cytologically-proven measurable, advanced adenocarcinoma of the pancreas or Ampulla of Vater. Metastases had to be confined to the abdominal cavity, e.g., peripancreatic lymph nodes, peritoneum, or liver metastases.

Other eligibility criteria included age > 18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate bone marrow function as defined by WBC $\geq$ 3,000/μl, absolute neutrophil count (ANC) > 1,500/μl, platelets > 100,000/μl; acceptable renal (serum creatinine $\leq$ 1.5 mg/dl) and hepatic (serum total bilirubin < 1.5 mg/dl, serum ALT and AST levels < 2 times the upper limit of normal) function; negative pregnancy test; and the ability to provide signed informed consent before protocol therapy.

Patients with one or more of the following criteria were excluded from the study: (1) any prior dFdC, 5-FU, or radiation therapy for pancreatic cancer; (2) any antitumor therapy within 30 days of protocol eligibility; (3) metastases outside the abdominal cavity; (4) concurrent malignancies other than non-melanoma skin cancers or cervical carcinoma in situ. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Pittsburgh and the National Institutes of Health.

Treatment plan and response assessment

This non-randomized, fixed-dose study examined a combined modality regimen of IP dFdC, IV dFdC, radiotherapy, and surgery (Fig. 1).

Prior to entry onto study, patients underwent a staging laparoscopy to define the extent of disease, assess resectability, and obtain tumor biopsies where possible. Patients were required to have disease that was not considered resectable for cure. This included patients with disease in peripancreatic structures, peripancreatic lymph node involvement, small volume peritoneal carcinomatosis, and/or liver metastases.

If patients were considered eligible at laparoscopy, a Tenchkoff catheter was inserted through the abdominal wall. Within 1 week of laparoscopy, patients underwent the first treatment of dFdC instilled through the Tenchkoff catheter into the peritoneal cavity. Treatment was delivered as four consecutive 6-h exchanges. Each exchange of dialysate contained 50 mg/m^2 dFdC in 2 l of commercial 1.5% dextrose dialysis solution and was instilled over 30–60 min via an infusion pump with warmer. The dose and schedule were based upon the maximum tolerated dose of systemically infused dFdC [2, 20]. At the end of the 24-h treatment period, patients received 2 l of 0.9% NaCl through the Tenchkoff catheter, which was immediately drained to irrigate any residual dFdC. Volumes evacuated after each 6 h dwell were not recorded. At the end of each 6 h peritoneal dwell, fluid was drained by gravity. Samples of peritoneal fluid and plasma were collected for pharmacokinetic analysis as described below. Patients were discharged from the hospital as appropriate and returned 1 week later for a second IP treatment identical to the first. The Tenchkoff catheter was removed after the second IP treatment.

Approximately 1–3 weeks after IP chemotherapy, patients began IV dFdC and external beam radiation. On Monday or Tuesday of each week, patients received 440 mg/m^2 of dFdC as a 30–60 min IV infusion. External

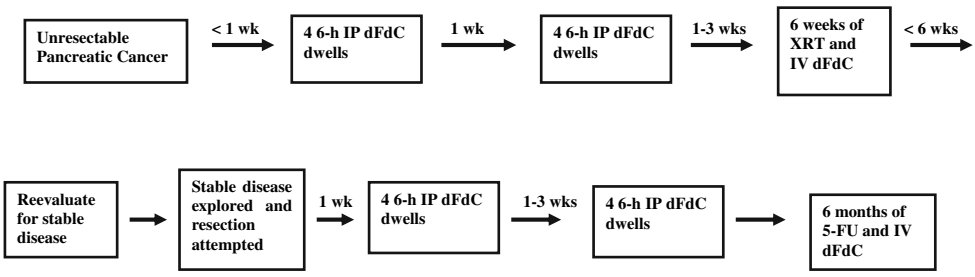

Fig. 1 Schema of multi-modality treatment of advanced pancreatic adenocarcinoma

IP = intraperitoneal, dFdC = gemcitabine, XRT = external beam radiation, 5-FU = 5-fluorouracil

beam radiation was given at a daily dose of 180 cGy/day, 5 days per week, for 6 weeks.

Within 6 weeks following IV dFdC and radiation therapy, patients were reevaluated for radiographic response and surgical resectability. Patients with progression of disease at the time of radiographic imaging were taken off study. Patients with stable or responding disease underwent exploration and resection as appropriate.

Two additional IP dFdC 4-dwell treatments, as previously described, were designed for patients remaining on protocol. Six months of dFdC and 5-FU maintenance therapy were scheduled to follow the second set of IP dwells.

The primary clinical endpoints were feasibility and toxicity. Overall survival and response represented secondary clinical endpoints. The study utilized the common toxicity criteria (CTC), version 2, for toxicity and adverse event reporting (http://ctepinfonih.gov). WHO criteria were used to categorize response.

Pharmacokinetic studies

Pharmacokinetic studies were performed during the first and second 24-h dFdC treatment periods. Samples of plasma were obtained from patients before, and at 15 min, 1 and 3 h after the first 6-h instillation of dFdC. Except for the pretreatment sample, samples of peritoneal fluid were obtained at the same times as plasma samples. Samples were also obtained immediately prior to and 15 min after each of the three subsequent IP instillations at 6, 12, and 18 h. Samples were also drawn at 24 h, which represented the end of the last 6-h dwell. At each time, 5 ml of blood was drawn into heparinized tubes that had been preloaded with 0.05 ml of a 10 mg/ml solution of the cytidine deaminase inhibitor, tetrahydrouridine (Calbiochem-Novabiochem Corp., La Jolla, CA). Blood samples were centrifuged for 10 min at approximately 1,000*g* and at room temperature. The resulting plasma was frozen and stored at −20°C until analysis. Samples (20–50 ml) of peritoneal fluid were collected in 50-ml conical centrifuge tubes that contained 0.5 ml of 10 mg/ml tetrahydrouridine, frozen, and stored at −20°C until analysis.

Concentrations of dFdC and dFdU were determined with a validated HPLC assay that was developed in our laboratories [32]. Authentic dFdC (Ly188011), dFdU (Ly198791), and 2′, 2′-difluorothymidine (Ly183997) internal standards were provided by Eli Lilly and Company (Indianapolis, IN).

Concentration versus time curves of gemcitabine and dFdU in plasma and peritoneal fluid were evaluated graphically. The area under the curve of peritoneal dFdC concentration versus time (AUC) was calculated using the log trapezoidal method.

Results

Clinical

Nine patients, six males and three females, with a median age of 60 years, were enrolled (Table 1). The head of pancreas was the most common site for pancreatic primaries (six patients). Two patients had primaries located in the pancreatic body, and one had a lesion in the tail of the pancreas (Table 1).

Three patients experienced grade 2 nausea, and one experienced grade 3 nausea, during the IP dFdC treatment period (Table 2). Nausea was easily controlled with antiemetics and did not result in prolonged hospitalization or require dose reduction. One patient experienced a grade 3 postoperative ileus, which resolved after conservative management with nasogastric tube decompression (Table 2). No hematological toxicities from IP therapy were noted.

Four patients had progression of disease after IP therapy and IV dFdC with radiotherapy and, therefore, were removed from the protocol. Five patients who were surgically

Table 1 Patients with locally advanced pancreatic cancer undergoing intraperitoneal gemcitabine

Pt	Sex	Age	Site of primary	Reason for unresectability
1	M	77	Head	Lymph nodes at ligament of Trietz
2	M	60	Head	SMV invasion
3	M	55	Body	Liver metastases
4	M	52	Body/tail	Celiac axis and gastric involvement
5	M	54	Head	Omental mass
6	F	58	Head	Peritoneal carcinomatosis
7	F	72	Head	SMV invasion
8	M	74	Tail	Peritoneal carcinomatosis
9	F	65	Head	SMV invasion

M male, *F* female, *SMV* superior mesenteric vein

Table 2 Toxicities and overall survival in patients treated with intraperitoneal gemcitabine (50 mg/m^2 q 6 h)

Patient	Toxicities	Survival (months)
1	Other—fever	14
2	Nausea Gr 2	23
3	Ileus Gr 3	17
4	None	16.5
5	Nausea Gr 2	27
6	None	18
7	None	17
8	Nausea Gr 2	12
9	Nausea Gr 3	7

Gr grade

Table 3 Management of patients after intraperitoneal gemcitabine and intravenous gemcitabine with external beam radiation

Patient	Surgery
1	Laparotomy, pancreaticoduodenectomy
2	Laparotomy and biopsy
3	Laparotomy and biopsy
4	PD (liver metastasis), no surgery
5	Laparotomy, LOA, biopsy
6	PD, no surgery
7	PD, no surgery
8	Laparotomy, distal pancreatectomy and splenectomy
9	PD, no surgery

PD progression of disease, *LOA* lysis of adhesions

explored after radiologic examination showed response or stable disease. Two of the patients explored were deemed surgically resectable and underwent pancreaticoduodenectomy and distal pancreatectomy, respectively (Table 3). Median overall survival of the nine patients enrolled in the trial was 17 months (range 7–27 months).

Pharmacokinetics

Low concentrations of dFdC were present transiently in the plasma of seven patients, and dFdC was not detected in the plasma of the other two (Fig. 2). Peak plasma dFdC concentrations rarely exceeded 1 μg/ml (Fig. 2). Plasma dFdU concentrations were low but increased gradually until 12 h and then declined little, if any (Fig. 3). IP dFdC concentrations declined quickly and were seldom detected prior to the next scheduled 6-h dwell (Fig. 4). dFdU concentrations in peritoneal fluid remained low throughout the treatment

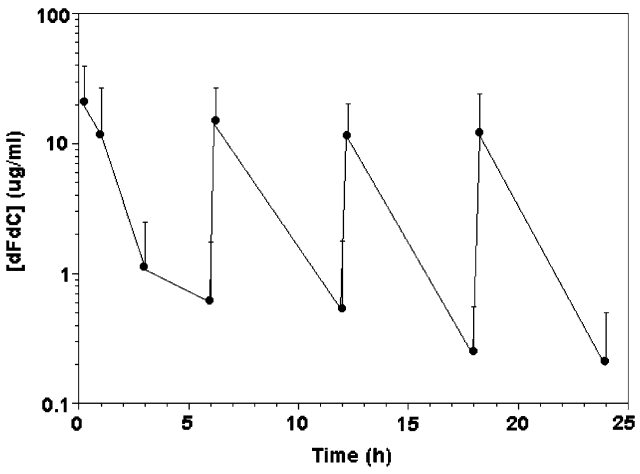

Fig. 2 Week one gemcitabine concentrations in peritoneal fluid of patients receiving 50 mg/m^2 intraperitoneal gemcitabine every 6 h. *Symbols* and *error bars* represent means and standard deviations, respectively

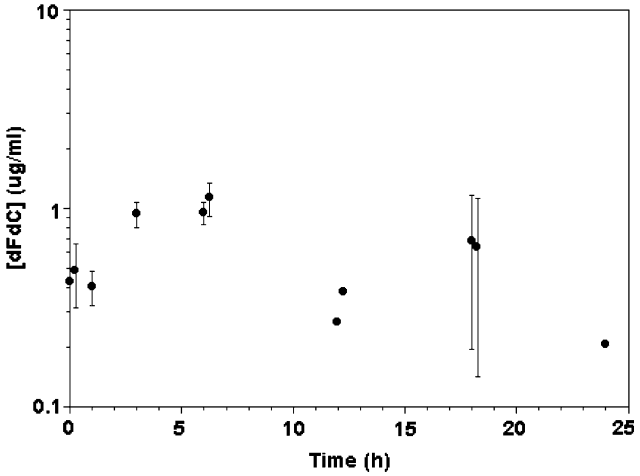

Fig. 3 Week one gemcitabine concentrations in plasma of patients receiving 50 mg/m^2 intraperitoneal gemcitabine every 6 h. *Symbols* and *error bars* represent means and standard deviations, respectively. If error bars are not present, then standard deviation was less than the symbol size

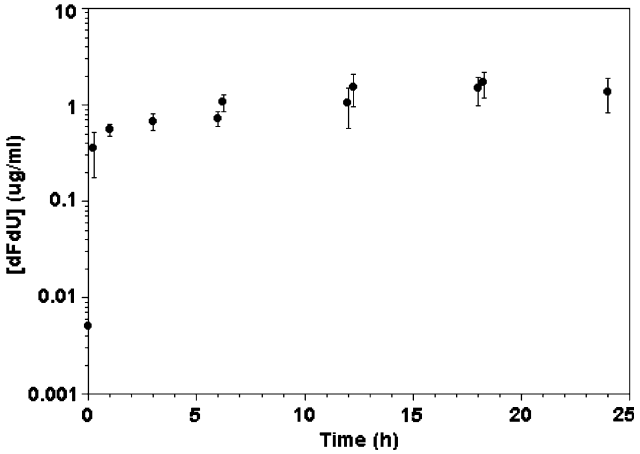

Fig. 4 Week one dFdU concentrations in plasma of patients receiving 50 mg/m^2 intraperitoneal gemcitabine every 6 h. *Symbols* and *error bars* represent means and standard deviations, respectively

(Fig. 5). The mean AUC for dFdC in peritoneal fluid was 182 μg/ml × h.

Discussion

IP dFdC administration has been reported in two previous studies [4, 33]. Sabbatini et al. [24] reported results from a study in which 75 mg/m^2 IP of cisplatin was delivered on day 1 in combination with escalating doses of IP dFdC on days 1, 8, and 15 every 28 days. Dose-limiting grade III thrombocytopenia was observed at 500 mg/m^2 dFdC. Pharmacokinetic evaluations demonstrated peritoneal fluid dFdC AUCs of 676–5,702 μM × h and indicated a 217–1,415-fold ratio of peritoneal fluid to plasma dFdC

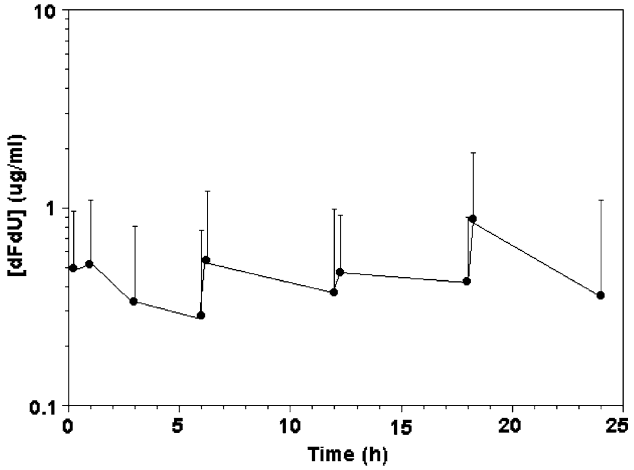

Fig. 5 Week one dFdU concentrations in peritoneal fluid of patients receiving 50 mg/m^2 intraperitoneal gemcitabine every 6 h. *Symbols* and *error bars* represent means and standard deviations, respectively

AUC. Additionally, Vyas et al. [33] reported initial results of a phase I study of IP gemcitabine using a weekly 1-h infusion. At 250 mg/m^2, they reported one patient with grade III neutropenia and one patient with grade III alkaline phosphatase elevation.

Rather than investigate the maximum tolerated dose of dFdC, we attempted to use multiple exchanges to achieve cytotoxic IP concentrations of dFdC for a prolonged period. The selection of 50 mg/m^2 in each of the four exchanges was a conservative dosing regimen, which exposed the peritoneal cavity to a total of 200 mg/m^2 over a 24-h period. The total dose was similar to the weekly dosing at 250 mg/m^2 by Vyas et al. [33]

Our study demonstrates the safety of IP dFdC administration for patients with locally advanced pancreatic adenocarcinoma. We instilled 50 mg/m^2 of dFdC in four 6-h exchanges to provide a continuous exposure to the peritoneal surfaces with little to no toxicity. The pharmacokinetic results of the study indicate a number of issues relevant to the clinical application of IP dFdC. The failure to observe dFdC in the plasma of two patients and the low concentrations seen in the remainder are expected when one considers the high CL_{tb} of dFdC, which reflects the large amount of cytidine deaminase present in liver, red cells, and other tissues. The exact mechanism behind the rapid decline of peritoneal dFdC concentrations and the low peritoneal concentrations of dFdU is unclear but the data imply almost total absorption of the drug. That the dFdC is converted extensively and rapidly to dFdU on the first pass, or subsequently, by cytidine deaminase-containing tissues is supported by the low plasma concentrations of the parent drug and the plasma concentration versus time profile of dFdU. The mean AUC for dFdC in peritoneal fluid was approximately 70× the previously reported dFdC peritoneal fluid AUC for a patient with ascites undergoing systemic dFdC treatment at 1,500 mg/m^2 [5]. These pharmacokinetic findings and lack of systemic toxicities in the current study provide an impetus for further evaluation of dFdC for IP therapy.

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