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CLINICAL TRIAL REPORT

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Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard hemodialysis treatment

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Abstract *Purpose*: Gemcitabine (2′,2′-difluorodeoxycytidine) is a cytotoxic agent with a low toxicity profile and proven activity against a number of solid tumors. It is not known whether gemcitabine is safe to administer to patients with kidney failure, and if dose adjustment is necessary. We determined the tolerability and pharmacokinetics of gemcitabine and its noncytotoxic metabolite 2′,2′-difluorodeoxyuridine (dFdU) in a patient with end-stage renal disease on maintenance hemodialysis therapy. *Patient and methods*: A 64-year-old patient with pancreatic cancer and end-stage renal disease received two cycles of gemcitabine at a standard dose of 1000 mg/m^2 given as a 30-min infusion on days 1 and 10. A regular 3.5-h hemodialysis treatment was performed 24 h after each infusion. Plasma and dialysate concentrations of gemcitabine and dFdU were determined by HPLC. The tolerability of gemcitabine treatment was assessed by clinical and laboratory parameters. *Results*: For gemcitabine, the maximal plasma concentration, terminal half-life ($t_{1/2}$) and area under the concentration-time curve (AUC) were similar to those reported for patients with normal renal function. In contrast, end-stage renal disease resulted in a five- to tenfold prolongation of terminal half-life and a distinct increase in the AUC of plasma dFdU in this patient. Plasma dFdU was effectively eliminated by hemodialysis treatment. Both cycles of gemcitabine were tolerated well with no unexpected side effects observed. *Conclusions*: Gemcitabine treatment in end-stage renal disease with intermittent standard hemodialysis treatment is safe and well tolerated. The pharmacokinetic data suggest that dose adjustment of gemcitabine should be avoided to ensure its full cytotoxic activity, and that hemodialysis treatment should be initiated 6–12 h after its administration to minimize the potential side effects of the metabolite dFdU.

Keywords Gemcitabine · End-stage renal disease · Pharmacokinetics

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Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine) is a synthetic pyrimidine nucleoside analogue with cytotoxic activity against a number of solid tumors. Objective antitumor responses have been documented for cancers of the pancreas, lung (small-cell and non-small-cell lung cancer), bladder, kidney, head and neck, breast, and ovary [5]. Gemcitabine is a prodrug which, after intracellular phosphorylation, exerts its cytotoxic effects through its active intracellular metabolites, gemcitabine di- and triphosphate. Whereas gemcitabine diphosphate inhibits de novo deoxyribonucleotide synthesis and thereby decreases the cellular nucleotide pool, gemcitabine triphosphate (dFdCTP) is incorporated into DNA, eventually leading to termination of DNA synthesis and cell death [5, 9].

After intravenous administration, gemcitabine is rapidly metabolized by deamination in the liver, kidneys and other tissues to a noncytotoxic metabolite, 2′,2′-difluorodeoxyuridine (dFdU). Peak dFdU plasma levels are observed 5–15 min after the end of the gemcitabine infusion and depend on the gemcitabine dose [1]. Elimination of dFdU is primarily renal and follows biphasic kinetics, with a terminal half-life of about 14 h [1]. Of the gemcitabine dose, 92–98% is recovered as dFdU in the urine, whereas less than 10% is recovered as the parent

compound. Metabolites of gemcitabine other than dFdU or elimination pathways of dFdU other than renal are of no quantitative relevance. Protein binding of gemcitabine and dFdU are approximately 50% each, i.e. relatively low. Both substances have a small distribution volume [5].

Numerous phase I studies of gemcitabine as a single agent have led to the dose recommendation of 1000 mg/m^2, administered as a weekly 30-min infusion [5, 9]. Using this treatment schedule, the toxicity profile of gemcitabine is low, with myelosuppression being the major side effect [4]. Extrahematological adverse events are usually mild and transient and include nausea and vomiting, a 'flu-like syndrome, elevation of serum transaminases, rash, edema and renal toxicity. In these pharmacokinetic and phase I trials, however, patients with impaired renal function were excluded and no dose recommendations exist for these patients (product information 2002, Eli Lilly and Company, Indianapolis, Ind.; http://pi.lilly.com/gemzar.pdf). In a first study addressing this problem, significant and partly unexpected toxicity even at reduced doses of gemcitabine was observed in patients with moderately impaired renal function (creatinine level 1.6–3.2 mg/dl) [10]. The underlying reason remained unclear, and caution or dose adjustment was recommended for gemcitabine treatment of this patient group [10].

We administered gemcitabine to a patient with advanced pancreatic cancer and end-stage renal disease (ESRD) on maintenance hemodialysis treatment, and determined relevant pharmacokinetic parameters and tolerability to assess the influence of renal function on the feasibility of gemcitabine treatment. We expected that complete loss of renal function in the patient would result in considerable accumulation of dFdU and possibly gemcitabine itself, but reasoned from their pharmacological properties that effective clearance could be achieved by hemodialysis treatment.

Patient and methods

Case report

A 64-year-old man was referred to our hospital in July 2001 because of obstructive jaundice, fever and chills. Ultrasonography and a CT scan revealed intra- and extrahepatic cholestasis caused by a locally advanced pancreatic tumor, as well as multiple intrahepatic lesions suggestive of liver metastases. To restore bile passage, an external percutaneous transhepatic cholangiographic drainage (PTCD) was implanted. Histopathological analysis of a biopsy taken from one of the intrahepatic lesions was consistent with a metastasis of a poorly differentiated pancreatic adenocarcinoma. The patient had a number of preexisting and coexisting diseases including hypertension, insulin-dependent diabetes mellitus, and coronary heart disease. After a myocardial infarction in 1996, coronary stenting (in the same year) and coronary bypass surgery (in February 2001) had been performed. He also suffered from chronic kidney failure with ESRD most likely due to nephrosclerosis, which had been treated with peritoneal dialysis since February 2000. After histopathological confirmation of the pancreatic cancer, the patient was switched from peritoneal dialysis to hemodialysis on a three-times weekly schedule.

He was then treated with two courses of gemcitabine at a dose of 1000 mg/m^2 (see below). The clinical course before, during and after chemotherapy was complicated by recurrent obstruction of the external bile drainage, which was followed by clinical and paraclinical signs of cholangitis, and made frequent change of the drainage and antibiotic therapy necessary. Additionally, a duodenal ulcer, possibly due to tumor invasion, was diagnosed before the start of the therapy and treated with proton pump inhibitors and intermittent erythrocyte transfusions. After the second course of chemotherapy the patient was discharged and discontinued further therapy cycles for personal reasons. For the same reasons, tumor response could not be evaluated by objective means. An increase in Karnofsky index from 50% before chemotherapy to 70% shortly thereafter indicated a modest clinical benefit response. He died about 3 months later, most likely from progressive tumor disease.

Patient treatment, hemodialysis and sample acquisition for HPLC analysis

Gemcitabine (Gemzar) was supplied by Eli Lilly Pharmaceuticals (Giessen, Germany) as a lyophilized powder and reconstituted with normal saline to a final concentration of 7.2 mg/ml. Before initiation of the treatment, informed consent was obtained from the patient for the treatment as well as for obtaining additional blood samples for pharmacokinetic analysis. Two courses of gemcitabine at a dose of 1000 mg/m^2 were administered on days 1 and 10 as 30-min infusions. For pharmacokinetic analysis, 10 ml blood was drawn into heparinized tubes before and 0.5, 1, 1.5, 2, 3, 5, 7, 9, 12 and 24 h after the start of the gemcitabine infusion. Samples were immediately processed by centrifuging at 1000 *g* at room temperature and the supernatant plasma was frozen at −20°C until analysis. Gemcitabine treatment days were fit into the hemodialysis schedule so that 24 h after chemotherapy a regular hemodialysis treatment could be performed. Bicarbonate hemodialysis lasted for a total of 3.5 h with a blood flow of 200 ml/min and a dialysate flow of 500 ml/min, using a polysulfone low-flux membrane (F7, Fresenius Medical Care, Bad Homburg, Germany). Blood samples were obtained and processed as above at the following time-points: immediately prior to and shortly after the initiation of the dialysis treatment, 2 h after the start of the treatment, at the end of the treatment, and about 3 h after the dialysis process was finished. Additionally, samples from the dialysate were obtained and frozen at −20°C briefly after the start of dialysis, 2 h after the start, and at the end of the treatment.

HPLC analysis

HPLC analysis was performed on an isocratic system using a 120 Å/5 µm C_{18} 250/4.6 mm reversed-phase column (Macherey-Nagel, Düren, Germany) equipped with a Waters M 510 solvent delivery system. For the detection of gemcitabine and dFdU, a Shimadzu SPD-6A UV detector was used at 275 nm. The analytical eluent consisted of 0.02 *M* KH_2PO4, 0.005 *M* pentanesulfonic acid (ion-pairing reagent), and 0.5% CH_3CN (v/v) adjusted to pH 2.0 with H_3PO4. The flow rate was 0.8 ml/min, and the column temperature was adjusted to 40°C with a water bath. Plasma samples were deproteinized using 10% perchloric acid (72%) for 500 µl plasma (v/v), vortex-shaken for 5 min and centrifuged at 1000 *g* for another 5 min. Supernatant (20 µl) was injected into the HPLC system using a Rheodyne 7725 equipped with a 20-µl sample loop. Hemodialysate samples were injected directly into the HPLC system without further preparation. As shown in Fig. 1, the retention times of gemcitabine and dFdU were 39 and 27 min, respectively, with an intra-assay variance of 18% and 15% at the detection limit of 100 ng/ml for both substances. At a median concentration of 1 µg/ml, the intra-assay coefficients of variation were below 10% for gemcitabine and for dFdU.

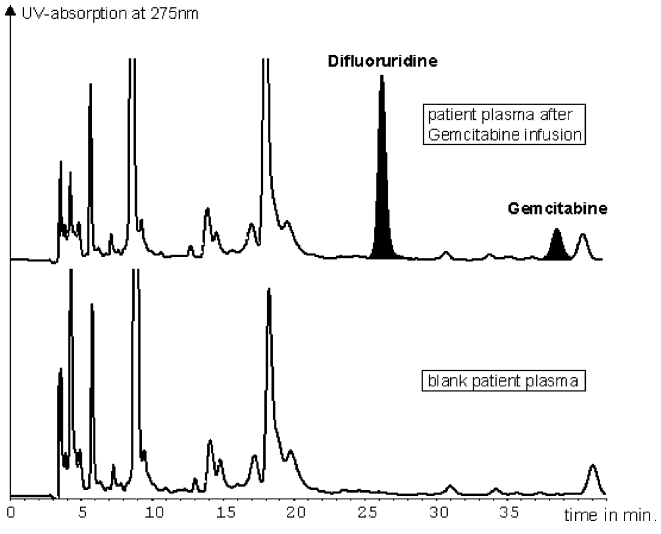

Fig. 1 HPLC separation of blank plasma and patient plasma after administration of gemcitabine

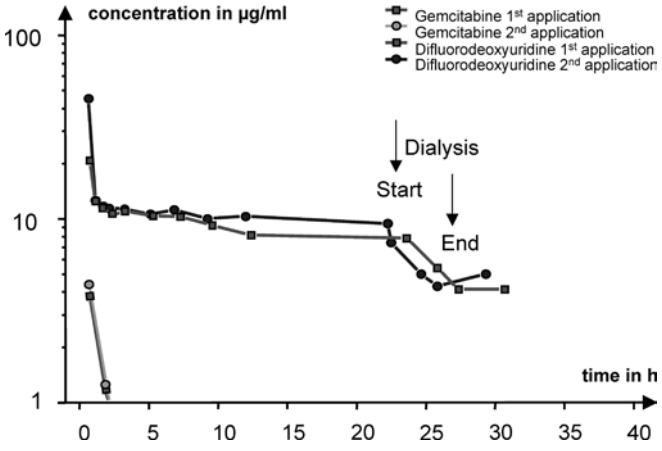

Fig. 2 Plasma decay curve of gemcitabine and dFdU after administration of 1000 mg/m^2 gemcitabine as a 30-min infusion. Note the logarithmic scale of the *y*-axis

Pharmacokinetic analysis

Analysis of the pharmacokinetic parameters was based on the TOPFIT computer program, providing an optimized adaptation of coefficients of variation between the observed and calculated data [6]. The total amount of dialyzed dFdU was estimated by multiplication of the AUC (0–3.5 h) by the flow of dialysate (30 l/h). The dialysis clearance of dFdU was estimated using the calculated amount of dFdU eliminated via dialysis and the plasma AUC of dFdU during the time window of dialysis, while the half-life of dFdU under dialysis represents the concentration decay during this time.

Results

The plasma concentrations of gemcitabine and dFdU after the first and second 30-min infusion of gemcitabine and the calculated pharmacokinetic parameters are shown in Fig. 2 and Table 1, respectively. No significant difference for any pharmacokinetic value was found between the two chemotherapy cycles.

For gemcitabine, plasma concentrations peaked at about 7 µg/ml and declined with the short elimination half-life ($t_{1/2}$) of 19 min. Compared to pharmacokinetic data from the literature [1, 2, 7], no apparent difference was found with respect to peak plasma concentration, elimination half-life, clearance or AUC (Table 1). This indicated that rapid metabolism of gemcitabine by cytidine deaminases of plasma and various tissues including liver and the kidneys [5] was not affected by the ESRD of the patient.

In contrast to the parent drug, plasma concentration kinetics of the metabolite dFdU followed a biphasic pattern, where an initial rapid distribution decline was followed by a second phase with a long terminal half-life of more than 60 h. As expected from its almost exclusive renal elimination pathway, the plasma clearance of dFdU in our patient, compared to patients with normal kidney function [1, 2, 7], was considerably reduced (29 vs 157 ml/min). Reduced clearance was paralleled by a prolongation of the elimination half-life by a factor of about five to ten, and a distinct increase in the AUC by a factor of about ten (Fig. 2, Table 1).

Standard hemodialysis treatment was able to effectively eliminate FdU from the plasma. A 3.5-h hemodialysis session starting 24 h after the gemcitabine infusion reduced plasma levels of dFdU by about 50% (Fig. 2), and accordingly dFdU was detected in the dialysate at concentrations of about 3 µg/ml at the beginning and 0.7 µg/ml at the end of each dialysis session (data not shown). The estimated amount of total eliminated dFdU calculated via the AUC of dFdU in the dialysate and the dialysis flow was 209 mg. Using this value and the AUC under the dFdU plasma decay curve at the time of dialysis, the half-life of dFdU was 3.9 h and the clearance was 148 ml/min (Table 1). Thus, the dFdU elimination half-life and clearance obtained by hemodialysis treatment were similar to values reported for patients with normal renal clearance [1, 2, 7] (Table 1). This indicates that dFdU is dialyzable, and that hemodialysis treatment can approximate normal kidney elimination from the patient plasma.

Gemcitabine treatment in this patient with ESRD was well tolerated. Toxicity was primarily hematological, with leukocyte nadirs of 2.7×10^6/l (WHO grade II) and 1.6×10^6/l (WHO grade III) observed after cycles 1 and 2 of gemcitabine treatment, respectively. Thrombocytopenia WHO grade II occurred after cycle 2. Hepatic toxicity was difficult to assess because of intermittent obstruction of the bile drainage (see above), but was transient and did not exceed WHO grade II. Cycle 2 of gemcitabine was followed by a febrile episode up to 39.4°C (WHO grade II), which was paralleled by obstruction of the bile flow and resolved after exchange of the PTCD. No unexpected side effects were observed.

Table 1 Pharmacokinetic parameters for gemcitabine and dFdU summarized from published data [1,2, 7] and calculated for the investigated patient (for details see Patient and methods) after administration of 1000 mg/m^2 gemcitabine over 30 min

		$t_{1/2}$	AUC (μg/ml h)	C_{max} (μg/ml)	Vc (l)	Cl_{total} (ml/min)	$Cl_{dialysis}$ (ml/min)	Cumulative elimination over 4 h (mg)
Gemcitabine	Normal renal function (reported data)	9–22.3 min	7.5–11.4	10.0–18.3	50–200	2550-4080		
	Complete renal failure (analyzed patient)	19 min	5.4	7.1	176	6150		
dFdU	Normal renal function (reported data)	5–16.5 h	73–121	23.6–28.2	50–150	157		
	Complete renal failure (analyzed patient)	62 h	1130	39	134	29		
	Under dialysis	3.9 h					148	209

Discussion

Many drugs, especially when they are eliminated primarily via renal pathways, require dose adjustment in patients with kidney failure in order to prevent accumulation of the drug and increased treatment toxicity [8]. Additional precautions apply for patients with ESRD because certain substances are not effectively eliminated by the patient's maintenance hemodialysis treatment. On the other hand, unexpected removal of some drugs by the dialysis procedure may lead to subtherapeutic plasma concentrations and subsequent treatment failure. In these cases, supplementation of the drug after each dialysis treatment is necessary [3]. Thus, in patients with kidney failure, detailed information about physical and pharmacokinetic properties of a given drug is necessary in order to avoid over- as well as undertreatment.

In cancer patients, impairment of kidney function is not uncommon and is often caused by previous cytotoxic treatment (e.g. chemotherapy or irradiation), coexisting diseases (such as hypertension or diabetes), or by the tumor itself. Whereas recommendations for dose and administration modalities for chemotherapeutic agents are generally based on large phase I pharmacokinetic and toxicity trials, patients with impaired kidney function are initially excluded. The relatively low numbers of patients with ESRD makes pharmacokinetic studies of cytotoxic drugs in this patient group particularly difficult. Consequently, for many chemotherapeutic agents, information about the optimal dosing and treatment schedule for patients suffering from various degrees of kidney failure is rare.

A typical example of this dilemma is the pyrimidine analogue gemcitabine, which in recent years has demonstrated cytotoxic activity against a number of solid tumors including pancreatic and non-small-cell lung cancer. In patients with normal kidney and liver function, gemcitabine is usually administered at a dose of 1000 mg/m^2 once weekly as a 30-min infusion, and under these conditions has a low toxicity profile. Regarding its use in patients with impaired renal function, no dose recommendations exist and caution is recommended by the manufacturer (product information 2002, Eli Lilly and Company, Indianapolis, Ind.; http://pi.lilly.com/gemzar.pdf). In a single reported study, gemcitabine was administered to 15 patients with moderate renal failure (creatinine level 1.6–3.2 mg/dl, median 1.8 mg/dl) [10]. Even at reduced doses of 650 mg/m^2 (six patients) and 850 mg/m^2 (nine patients), four of the 15 patients experienced significant side effects, including two cases of severe skin toxicity (diffuse erythema and desquamation). The underlying mechanism was unclear. Compared to a control cohort with liver dysfunction, renal disease in this study was paralleled by about a two- to threefold increase (albeit non-significant) in dFdU AUC; however the impact of dFdU accumulation and/or other characteristics of

renal dysfunction on the observed side effects remained unclear [10]. The authors concluded that gemcitabine in patients with renal dysfunction should be used cautiously and with dose reduction.

We approached the problem of gemcitabine toxicity in patients with renal dysfunction using an extreme example of ESRD. We found that renal dysfunction did not lead to accumulation of gemcitabine itself, because none of the pharmacokinetic parameters we determined appeared to be affected by the ESRD of our patient. Even though we did not determine intracellular levels of gemcitabine's cytotoxically active triphosphate dFdCTP, they are known to depend on gemcitabine concentrations and moreover to reach a plateau with gemcitabine plasma concentrations exceeding 5 μg/ml or 15–20 μ*M* [1]. Thus, neither gemcitabine nor dFdCTP are likely to contribute to gemcitabine's toxicity in patients with kidney failure directly. In contrast, and given its not unexpected almost exclusively renal elimination pattern, plasma clearance of the noncytotoxic metabolite of gemcitabine, dFdU, was considerably reduced in our patient with ESRD. The result was an AUC which, compared to values reported in the literature [1, 2, 7], was increased about tenfold. It is considered that dFdU is not cytotoxic. However, given its considerable accumulation with renal dysfunction (as shown in this study), it cannot be excluded that high levels of dFdU in patients with renal disease, either directly or indirectly, may cause undesired side effects. Further studies are desirable to address the question as to whether accumulation of dFdU is clinically relevant, and whether dialysis treatment in patients with renal dysfunction is both necessary and sufficient to preclude toxic side effects of gemcitabine treatment.

Based on our finding of its unaltered pharmacokinetics in ESRD, dose reduction of gemcitabine in patients with renal dysfunction appears not only to be unnecessary but disadvantageous, because it may result in a loss of cytotoxic activity against the tumor. On the other hand, removal of dFdU (and, potentially, other accumulating metabolites) from plasma to levels found in patients with normal renal function may effectively diminish the toxic side effects. The fact that gemcitabine treatment was well tolerated by our patient without any unexpected adverse events is consistent with this hypothesis. As shown in this study, dFdU is dialyzable with a clearance of about 100–150 ml/min and therefore can be effectively removed from the plasma in a timely manner approximating normal renal function. The hematological toxicity we observed is within the reported range [4], but needs to be carefully monitored in further patients.

The present data are from a single patient and therefore require confirmation. However, we believe that some important preliminary conclusions can be drawn. First, treatment of cancer patients with renal dysfunction at all stages in which a therapeutic benefit of gemcitabine as a single-agent chemotherapeutic drug would be expected, is safe and can be encouraged, provided a standard hemodialysis treatment can be performed afterwards. Second, these data from a single patient suggest that gemcitabine should be administered without dose reduction in order to avoid loss of cytotoxic efficacy and undertreatment of the tumor. Third, hemodialysis treatment is sufficient to remove gemcitabine's deamination product dFdU from the plasma. Based on the observation that gemcitabine is completely metabolized to its active intracellular bi- and triphosphates within a few hours (Fig. 2), dialysis treatment can be initiated as early as 6 h after chemotherapy without loss of cytotoxic efficacy. The optimal starting time, duration and intervals need to be determined in further studies.

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