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ORIGINAL ARTICLE

# A phase I study of gemcitabine given via intrahepatic pump for primary or metastatic hepatic malignancies

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**Abstract**
*Purpose* To determine the maximum tolerated dose and duration of hepatic arterial infusion (HAI) gemcitabine in patients with unresectable hepatic metastases from colorectal cancer or primary hepatic malignancies.
*Methods* Patients received weekly gemcitabine via the side-port of an implantable HAI pump for 3 weeks in a 28-day cycle. During the dose escalation phase, increasing doses of HAI gemcitabine (800, 1,000, 1,200, and 1,500 mg/m$^2$) were given at a fixed dose-rate of 10 mg/(m$^2$ min). This was followed by the infusion duration escalation (IDE) phase, in which HAI gemcitabine at 1,000 mg/m$^2$ was given over increasing lengths of time (200, 300, and 400 min). To estimate hepatic drug extraction, the pharmacokinetics of HAI gemcitabine was compared with those of intravenous gemcitabine given at the same dose-rate to the same patient in the IDE phase.
*Results* Twenty-eight of 30 patients were evaluable. HAI gemcitabine was well tolerated up to 1,500 mg/m$^2$ given at 10 mg/(m$^2$ min) and up to 1,000 mg/m$^2$ infused over 400 min. There were no protocol-defined dose-limiting toxicities. One patient with cholangiocarcinoma had a partial response. Hepatic extraction of gemcitabine seems highly variable among patients and does not correlate with the length of HAI infusion.
*Conclusions* Hepatic arterial infusion of gemcitabine given at doses higher or longer than the recommended systemic dose of 1,000 mg/m$^2$ over 30 min is well tolerated. For future studies, we recommend an infusion of 1,500 mg/m$^2$ at a fixed dose-rate of 10 mg/(m$^2$ min).

**Keywords** Gemcitabine · Hepatic arterial infusion · Cholangiocarcinoma

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## Introduction

About 150,000 cases of colorectal cancer are diagnosed each year in the United States, and 50–60% of these patients develop distant disease, with the liver as the only site of metastasis in a third of the cases [15]. Primary liver cancer consists mainly of hepatocellular carcinoma and cholangiocarcinoma, both of which are increasing in incidence, affecting approximately 20,000 individuals annually in this country [15]. Thus, primary liver cancers and hepatic metastases from colorectal cancer that are confined to the liver comprise a substantial portion of gastrointestinal malignancies.

For colorectal cancer, complete surgical resection is a potentially curative treatment in patients with liver-only metastases, producing a 5-year survival rate of 27–39% and an actual cure rate of 17% [13, 27]. For patients with hepatocellular carcinoma and good hepatic reserve, partial hepatectomy has been standard therapy. When complete resection is not feasible because of the location or number of the tumors, other local modalities of therapy, such as tumor embolization and/or radiofrequency ablation, have been employed [8, 20, 31].

Hepatic arterial infusion (HAI) therapy represents another liver-directed treatment option [9, 28]. The use of

HAI is based on sound physiology and pharmacology. First, liver metastases that grow beyond 2–3 mm depend on the hepatic artery for vascularization, whereas normal liver tissues are perfused by the portal vein [3, 7]. Second, HAI therapy allows delivery of increased local concentration of cytotoxic agents to hepatic metastases not achievable by systemic administration, especially for drugs with high systemic clearance [10]. Third, first-pass hepatic extraction of certain drugs results in lower systemic concentrations and hence, less systemic toxicities. Floxuridine (5-fluoro-2′-deoxyuridine, FUDR) is an example of such a drug, 94–99% of which is extracted by the liver during the first pass [11, 12]. Randomized trials comparing HAI of FUDR to systemic chemotherapy in patients with metastatic colorectal cancer have demonstrated superior response rates and time to hepatic progression for unresectable disease, and have shown improved time to progression and overall survival in the adjuvant setting following hepatic resection [17, 18].

One drawback of HAI FUDR is hepatobiliary toxicity, with elevation of liver enzymes or bilirubin occurring in 42% of patients in early randomized trials [25]. While the incidence of severe hepatic toxicity can be reduced by co-administration of dexamethasone, mild to moderate liver function abnormalities are common, requiring frequent dose attenuations. Development of alternative HAI agents with improved toxicity profiles may provide new therapeutic options for patients with hepatic metastases or primary liver malignancies.

Gemcitabine (2′,2′-difluorodeoxycytidine) is a pyrimidine antimetabolite structurally similar to cytarabine [22] a pro-drug that requires intracellular phosphorylation to the active 5′-triphosphate by deoxycytidine kinase. Cytotoxicity of gemcitabine is mediated primarily by its effects on DNA replication via: (1) incorporation of gemcitabine triphosphate into DNA, resulting in slowing of replication fork progression; (2) inhibition of ribonucleotide reductase by gemcitabine diphosphate, causing deoxyribonucleotide pool depletion; and (3) direct inhibition of replicative DNA polymerases by gemcitabine triphosphate [22]. Gemcitabine is cleared through metabolic elimination by cytidine deaminase and cytidylate deaminase; both are abundant in the liver [24]. Gemcitabine exhibits linear pharmacokinetics (PK) with a half-life of 11–26 min when a short infusion schedule is used (<70 min). With longer infusion times, the half-life varies from 18.5 to 57.1 min, which has been attributable to increased tissue distribution [1]. As a single agent, gemcitabine is well tolerated and exhibits a broad spectrum of activity in solid tumors, including non-small cell lung, breast, pancreas, bladder, and ovarian cancers. Gemcitabine has been evaluated in patients with advanced biliary cancer in several phase II studies, with response rates reported at 8–36% [21].

The "regional advantage" of an agent given by HAI over an intravenous (IV) infusion is proportional to the systemic clearance and hepatic extraction of the drug [11]. In view of its high systemic clearance [1] and possibly high hepatic extraction[24], gemcitabine may be a good candidate for HAI therapy.

Vogl et al. [30] reported a phase I study of HAI gemcitabine with or without microspheres administered in patients with intra-hepatic cholangiocarcinoma or metastases from pancreatic cancer. Gemcitabine was given on day 1 and 8 of each 28-day cycle via a percutaneously placed catheter over ≤20 min. The maximum tolerated dose (MTD) of gemcitabine without or with microspheres was determined to be 1,400, and 1,800 mg/m$^2$, respectively. There were no complete/partial responses, although 20 of 24 evaluable patients had stable disease as the best response.

In this phase I study, we examined the tolerability and PK of HAI gemcitabine given via an implantable pump. In the first phase (dose-escalation phase) of this study, increasing doses of gemcitabine were given at a fixed rate of 10 mg/(m$^2$ min) in order to maximize intracellular accumulation of gemcitabine triphosphate in tumors. In the second phase (infusion duration-escalation phase), patients received a fixed dose of HAI gemcitabine administered over an increasing duration of infusion, i.e., decreasing dose-rate. We hypothesized that a prolonged intrahepatic infusion of gemcitabine at a lower dose-rate might increase its cytotoxicity and meanwhile avoid saturation of hepatic clearance, thereby minimizing systemic toxicity.

## Patients and methods

### Patient eligibility

Patients with histologically confirmed adenocarcinoma metastatic to the liver, or hepatocellular carcinoma or suspected intrahepatic cholangiocarcinoma, were considered eligible. Liver metastases had to be deemed unresectable and comprise <70% of the liver parenchyma. Extrahepatic disease was permissible if it was minimal and if local treatment to the liver was a safe option according to the treating investigator. Prior systemic treatment with gemcitabine was allowed. Other eligibility criteria included age ≥ 18 years, KPS ≥ 60%, WBC ≥ 3,000 cells/mm$^3$, platelet count ≥100,000 cells/mm$^3$, albumin >2.0 gm/dl, total bilirubin <2.0 mg/dl, and prothrombin time within 1.5 s of normal. Pregnant or lactating patients were excluded, as were those who had radiation within 4 weeks, prior radiation to the liver, active infection, ascites, hepatic encephalopathy, or untreated brain metastases. All patients had to have an implantable hepatic artery pump already in place.

### Study design and treatment plan

This open-labeled, nonrandomized phase I study consisted of two phases: dose escalation (DE) and infusion duration escalation (IDE). All HAI gemcitabine treatments were administered through the side-port of an implantable pump via an external infusion system. In the DE phase, increasing doses of gemcitabine were given at a fixed rate of 10 mg/($m^2$ min) via the side port of an intrahepatic pump every week for 3 of 4 weeks. The planned dose levels of gemcitabine were 800, 1,000, 1,200, and 1,500 mg/$m^2$. Once the MTD of HAI gemcitabine had been established (see below) in the DE phase, the IDE phase commenced, in which patients received a fixed, normalized dose of intrahepatic gemcitabine over an increasing duration of infusion (i.e., decreasing dose-rate) every week for 3 of 4 weeks. Three dose-rate de-escalations were planned: 5, 3.33, and 2.5 mg/($m^2$ min). The dose of gemcitabine given in the IDE phase was the MTD of gemcitabine established in the DE phase reduced by two dose levels.

To compare the PK of intrahepatic gemcitabine with that of IV gemcitabine, patients enrolled in the IDE phase also received IV gemcitabine on day −7 during the first course of therapy; gemcitabine was given intrahepatically thereafter. Intravenous gemcitabine was given at the same dose-rate as subsequent intrahepatic treatments, but over an attenuated duration (only 60 min) to avoid undue toxicities associated with a prolonged infusion.

### Toxicity assessment and dose modifications

A minimum of three patients were followed for at least one complete cycle of therapy before DE to the next level. If a dose-limiting toxicity (DLT) was observed, the cohort was expanded to three additional patients. The MTD was defined as the highest dose level or longest duration of infusion, with DLTs seen in no more than one of six patients. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria v.3. Dose-limiting toxicity was defined as the occurrence of grade 4 neutropenia or thrombocytopenia; febrile neutropenia (ANC < 1,000/$mm^3$ and fever ≥38.5°C); ≥grade 3 non-hematological toxicity except for alopecia, nausea, or vomiting; ≥grade 3 diarrhea despite aggressive use of loperamide; total bilirubin ≥ 3.0 mg/dl not caused by disease progression; and any delay in treatment for >7 days. Hepatic toxicity from treatment was defined as a significant increase over individual baseline values (≥1.5-fold for alkaline phosphatase (Alk Phos), ≥4-fold for aspartate aminotransferase (AST), and ≥1.5-fold for bilirubin). Liver enzymes elevations were managed with treatment hold or modifications as discussed below, and not considered dose-limiting unless there was a concomitant elevation of total bilirubin ≥3.0 mg/dl. Patients were evaluated for DLTs during cycle 1 of intrahepatic gemcitabine treatment. Toxicity following IV gemcitabine administration was not considered dose limiting.

Dose modifications of gemcitabine for drug-related elevation of liver enzymes were made, similar to those previously described for hepatotoxicity induced by HAI FUDR [16]. Gemcitabine dose was reduced by two levels if AST, Alk Phos, or total bilirubin were abnormally elevated to 4–5, 1.5–2, and 1.5–2 times the reference value, respectively, defined as the value obtained on the day when the most recent gemcitabine dose was given. Treatment was held if AST, Alk Phos, or total bilirubin was elevated to ≥5, ≥2, and ≥2 times of the reference value, respectively. In that case, treatment could be resumed at −2 dose levels if AST, Alk Phos, and total bilirubin recovered to within 4, 1.5, and 1.5 times the reference value, respectively. If a patient experienced a grade 3 hematological toxicity (leucopenia, neutropenia, or thrombocytopenia), therapy was held until recovery to grade ≤ 1, then resumed at −1 dose level. Doses held during a cycle were not made up except during cycle 1. In the event of a DLT, treatment could be resumed at −2 dose levels upon recovery from toxicity at the discretion of the investigator. It was gemcitabine dose rather than infusion duration that was decreased with each dose reduction.

### On-study evaluations

Pretreatment evaluation consisted of a complete history, physical examination, and laboratory studies, including complete blood count (CBC), blood urea nitrogen, creatinine, total bilirubin, Alk Phos, AST, albumin, lactate dehydrogenase, and tumor markers (when appropriate) within 1 week before commencing chemotherapy. Liver enzymes, total bilirubin, and CBC were monitored every week. Radiological evaluations were obtained at baseline and 8-week intervals; assessments were made based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [26].

### Pharmacokinetics

All blood samples were obtained from a peripherally inserted venous catheter. During DE, patients underwent plasma PK samplings at the following time points: pre-dose, 0, 0.5, 1, 2, end of infusion, and 24 h after initiation of gemcitabine. During IDE, patients received a 60-min infusion of IV gemcitabine on day −7 of cycle 1 and underwent samplings at pre-dose, 0.5, 1, 1.5, and 2 hours. On day 1 of cycle 1, plasma was sampled at pre-dose, 1, 2, 4 h (if infusion time was ≥4 h), end of HAI gemcitabine, and 15, 30, and 60 min after end of infusion. At each time point, blood

samples (10 ml) were collected into heparinized tubes containing 1 mg of tetrahydrouridine. Following centrifugation at 2,000×*g* for 20 min, plasma was separated and refrigerated at −20°C until analysis.

Plasma concentrations of gemcitabine were determined as previously described, with modifications [19]. Prior to injection into the chromatography column, thawed plasma samples were passed through a Millipore Ultrafilter (10,000 cutoff molecule weight) to remove proteins. Analysis of plasma gemcitabine was carried out using a high-performance liquid chromatography system on a 250-mm Inertsil ODS-3 column (inner diameter, 4.6 mm; particle size, 5 micron) [19]. Compounds were eluted with an isocratic mobile phase consisting of 2% acetonitrile in 10 mM phosphate buffer (pH 3) at 1.0 ml/min, and quantified by ultraviolet absorbance at 265 nm. Calibration curves were prepared by analysis of plasma spiked with a known amount of gemcitabine standard.

Gemcitabine concentrations determined in the DE phase were compared with simulated gemcitabine concentrations obtained using population PK parameter estimates derived from a pooled analysis of s PK studies conducted in 353 subjects [2]. Simulations were carried out on the demographics of those recruited in this study, as insufficient patient numbers prevented characterization of the covariate distribution model. Population PK parameters included in the simulations were dose, gender, age, weight, body surface area, and serum creatinine. One thousand data sets were simulated with gemcitabine concentrations predicted at hourly intervals from time 0 to 24 h using NONMEM Version V Release 1.1 software (GloboMax LLC, Ellicott City, MD). Additional predictions were made at 0.5 hours and at the end of the infusion for each of the four dose groups, i.e., 1.33, 1.67, 2, and 2.5 h after initiating the infusion.

The plasma gemcitabine concentrations obtained at 1 hour after the initiation of IV were compared with those after HAI treatment using a paired Wilcoxon test.

**Table 1** Patient Demographics

| Demographics | DE | IDE | Total (DE + IDE) |
|---|---|---|---|
| No. of patients treated | 16 | 14 | 30 |
| No. of pts evaluable for toxicity | 16 | 12 | 28 |
| No. of pts evaluable for response | 16 | 12 | 28 |
| Median age (years) (range) | 65 | 58 | 64 |
| Male:female ratio | – | – | 18:12 |
| Median baseline KPS (%) (range) | 90 (80–90) | 80 (70–90) | 90 (70–90) |
| Median no. of prior chemotherapy treatments (range) | 2 (1–4) | 2 (1–5) | 2 (1–5) |
| Primary disease sites | | | |
| Colorectal | 16 | 4[a] | 20 |
| Cholangiocarcinoma | 0 | 6 | 6 |
| Hepatocellular carcinoma | 0 | 4 | 4 |

*DE* dose escalation, *IDE* infusion duration escalation

[a] One patient with metastatic small bowel adenocarcinoma was enrolled after obtaining approval from Institution Review Board

**Table 2** Dose and infusion duration escalation cohorts with HAI gemcitabine

| Cohorts | HAI gemcitabine dose (mg/m$^2$) | Dose-rate [mg/(m$^2$ min)] | Infusion time (min) |
|---|---|---|---|
| DE | | | |
| 1 | 800 | 10 | 80 |
| 2 | 1,000 | 10 | 100 |
| 3 | 1,200 | 10 | 120 |
| 4 | 1,500 | 10 | 150 |
| IDE | | | |
| 1 | 1,000 | 5 | 200 |
| 2 | 1,000 | 3.3 | 300 |
| 3 | 1,000 | 2.5 | 400 |

*DE* dose escalation, *IDE* infusion duration escalation

## Results

Thirty patients entered the study; 28 were evaluable for toxicity and response. Their demographics are listed in Table 1. All patients were previously treated with HAI FUDR. Six patients treated in the IDE phase had previously received systemic gemcitabine. The total number of HAI gemcitabine cycles given in DE and IDE were 43 and 36, respectively. The median number of cycles delivered in the DE and IDE phases were 2 (range 1–6) and 3 (range 1–11), respectively. One patient withdrew consent before completing cycle 1, and another patient developed grade 2 flu-like symptoms after IV gemcitabine; both were replaced. In the DE phase, HAI gemcitabine was escalated to the highest planned dose of 1,500 mg/m$^2$ without DLTs. Accordingly, the starting HAI gemcitabine dose in the IDE phase was therefore 1,000 mg/m$^2$ (MTD of DE phase −2 dose levels). The infusion duration of HAI gemcitabine was also escalated to the longest planned duration of 400 min without DLTs. The dose levels, dose-rates, and infusion time of HAI gemcitabine given in DE and IDE phases are shown in Table 2.

One patient treated in cohort IDE-1 was removed from study after cycle 6 because of worsening of a pre-existing neurological condition (Lewy body disease). His cognitive function continued to decline after discontinuation of HAI

**Table 3** Incidence of grade 2 or higher adverse events (cycle 1 only) with HAI gemcitabine

| Cohorts | No. of pts | Leukopenia | | | Neutropenia | | | Thrombo-cytopenia | | | AST | | | Alk phos | | | Total bilirubin | | | Fatigue | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 |
| DE | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 4 | 2 | – | – | 2 | – | – | – | – | – | – | – | – | 1 | 1 | – | – | – | – | – | – | – |
| 2 | 4 | 1 | – | – | 1 | – | – | – | – | – | – | – | – | – | 1 | 1 | – | – | – | 1 | – | – |
| 3 | 4 | 2 | 1 | – | 1 | 1 | – | 1 | - | – | – | – | – | – | – | – | – | – | – | 1 | – | – |
| 4 | 4 | 3 | – | – | 3 | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | – |
| IDE | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 6 | 1 | 1 | – | 1 | 3 | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – |
| 2 | 3 | – | – | – | – | – | – | 1 | 1 | – | – | – | – | 2 | – | – | – | – | – | – | – | – |
| 3 | 3 | 1 | 1 | – | – | 1 | – | 1 | 1 | – | – | – | – | – | – | – | – | – | – | – | – | – |

*DE* dose escalation, *IDE* infusion duration escalation, *G* grade, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase

**Table 4** Incidence of grade ≥ 2 adverse events (all cycles) with HAI gemcitabine

| Cohorts | No. of patients | Leukopenia | | | Neutropenia | | | Thrombo-cytopenia | | | AST | | | Alk phos | | | Total bilirubin | | | Fatigue | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 |
| DE | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 4 | 1 | – | – | 2 | – | – | – | – | – | – | – | – | 1 | 1 | – | – | – | – | – | – | – |
| 2 | 4 | 1 | – | – | 1 | – | – | – | – | – | – | 1 | – | – | 1 | 1 | – | – | – | 1 | – | – |
| 3 | 4 | 2 | – | – | 1 | 1 | – | 1 | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – |
| 4 | 4 | 2 | – | – | 3 | – | – | 1 | 2 | – | – | 1 | – | – | – | – | – | – | – | – | – | – |
| IDE | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 6 | 2 | 1 | – | 1 | 3 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 2 | 3 | – | – | – | – | – | – | 2 | 1 | – | – | – | – | 2 | – | – | – | 1 | – | 1 | – | – |
| 3 | 3 | 1 | 1 | – | – | 2 | – | 1 | 1 | – | – | – | – | – | – | – | – | – | – | – | – | – |

*DE* dose escalation, *IDE* infusion duration escalation, *G* grade, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase

therapy. After two cycles, another patient treated in the same cohort was taken off study for social reasons. One patient enrolled in cohort IDE-3 experienced abdominal pain upon usage of the HAI pump during cycle 4. A diagnostic arteriogram obtained after injection of contrast into the pump reservoir revealed dissection from the tip of pump catheter to the right hepatic artery stump and common hepatic artery without extravasation of contrast. The patient was removed from the study. This represents the only catheter-related adverse event.

## Tolerability

Twenty-eight patients were assessable for toxicity. Grade ≥ 2 adverse events that were considered at least possibly related to therapy are listed in Tables 3 and 4, respectively. There were no protocol-defined DLTs observed in the DE or IDE phase.

Major grade 3 + toxicities included leucopenia (21%), neutropenia (7%), thrombocytopenia (14%), AST (7%), Alk Phos (7%), and bilirubin (4%). Liver function abnormalities were relatively uncommon in the IDE phase. Conversely, grade 3 neutropenia and thrombocytopenia seemed to be more common in the IDE than DE phase (Tables 3, 4).

Elevations in hepatic enzymes (AST and Alk Phos) and total bilirubin associated with HAI therapy were managed using a similar algorithm previously utilized for hepatic toxicity induced by FUDR (see "Patients and methods") [16]. Five patients experienced grade ≥ 3 liver enzyme elevation during the study, two of whom had an event during cycle 1 (Tables 3, 4). Four of the five patients with hepatic toxicity received treatment in the DE phase. We observed one grade 3 total bilirubin, one grade 3 AST, two episodes of grade 3 Alk Phos, and one episode of grade 4 Alk Phos in conjunction with grade 3 AST. Using the above-mentioned dose-modification algorithm, no patient developed a biliary stricture or required a treatment hold because of hepatic toxicity for >14 days, which would be considered a DLT for this study.

Among other significant toxicities, there was an incidence of grade 3 papulomacular skin rash on the torso of a

patient treated during cycle 1. The rash resolved spontaneously within 1 week and did not recur upon resumption of treatment after dose reduction. Because of the idiosyncratic nature of the rash, this event was not considered a DLT. One patient developed grade 2 diarrhea during cycle 3, one had grade 2 lower extremity edema that responded to diuretics, and one patient developed grade 2 creatinine elevation.

Eleven of 28 evaluable patients (39%) required at least one dose reduction during cycle 1. Five patients had a dose reduction in the DE phase (hepatic toxicity in four patients and skin toxicity in one patient), whereas dose was reduced for six patients in the IDE phase due to myelosuppression. Eleven patients were able to receive full dose HAI gemcitabine for three consecutive weeks without delays in cycle 1. In the DE phase, the total cumulative dose of HAI gemcitabine given during the first 4 weeks of treatment was 2,300, 2,850, 3,550, and 3,975 mg/m$^2$ at the 800, 1,000, 1,200, and 1,500 mg/m$^2$ dose level, respectively. In the IDE phase, the total cumulative dose was 2,400, 2,870, and 2,530 mg/m$^2$ at the dose-rate of 5, 3.3, and 2.5 mg/m$^2$/min, respectively.

## Pharmacokinetic analysis

Pharmacokinetic data were collected from 14 subjects treated in the DE phase. Seven subjects had gemcitabine concentrations collected on two separate occasions, with an identical dose given on each occasion. Fifty-one concentrations were available for analysis. Plasma gemcitabine concentrations were simulated using PK parameters estimated from a NONMEM analysis of 7 pooled studies of IV gemcitabine conducted in 353 patients (Table 5) [2]. A pooled, nonlinear mixed effects analysis of the pooled PK data suggests a two-compartment model with proportional error that best describes the PK of gemcitabine. The results of simulated gemcitabine concentrations overlaid with observations from this study are shown in Fig. 1. All dose groups are represented by Fig. 1a, with individual dose groups shown in Fig. 1b. Thirty-nine percent of observed concentrations fell outside the 10th to 90th predicted interval range, with 8% of these in each of the 800, 1,200, and 1,500 mg/m$^2$ dosing arms and 16% in the 1,000 mg/m$^2$ dosing arm. Eighteen observations (35%) were below the 10th percentile of the prediction interval, whereas only two observations (4%) were above the 90th percentile of the prediction interval.

These results indicate that the observed gemcitabine concentrations following HAI were generally lower than values predicted from population PK parameters of IV gemcitabine, providing preliminary evidence for hepatic extraction of the drug when given directly into the liver.

Assuming a hepatic arterial and portal venous blood flow of 300 and 1,000 ml/min, respectively [11], an infusion of gemcitabine delivered at 10 mg/(m$^2$ min) into the hepatic artery of a patient with a body surface area of 1.95 m$^2$ is estimated to produce a local concentration of 40–200 μM gemcitabine, depending on the relative contribution of hepatic arterial and portal venous system to the tumor vasculature. Such a high local concentration may saturate the capacity of hepatocytes to metabolize gemcitabine. We therefore postulated that a more prolonged HAI gemcitabine given at a lower dose-rate may maximize hepatic drug extraction and thereby minimize systemic toxicity, meanwhile increasing exposure of tumors to the S-phase-specific effect of the drug.

In order to test our hypothesis, patients in the IDE phase of the study received HAI gemcitabine at 1,000 mg/m$^2$ over an increasing duration of infusion (i.e., at a decreasing dose-rate; Table 2). For a comparison of plasma gemcitabine levels obtained by HAI with those following systemic administration, patients received IV gemcitabine during the first course of treatment (day −7) at the same

**Table 5** Pharmacokinetic parameter estimates from pooled analysis of seven IV gemcitabine studies ($N$ = 353)

| Parameter (U) | Population mean | | Between subject variability | |
|---|---|---|---|---|
| | Estimate | % SEM | Estimate | % SEM |
| CL [l/(h m$^2$)] | 122[a,b] | 22 | 52 | 30 |
| $V_c$ (l/m$^2$) | 17.5[c] | 9 | 92 | 25 |
| $Q$ (l/h) | 225 | 11 | 85 | 18 |
| $V_p$ (l/m$^2$) | 370[d] | 19 | – | – |
| Error (% CV) | 41 (% CV = 10) | | | |

*IV* intravenous, *SEM* standard error of the mean, *CL* clearance, $V_c$ volume of distribution of central compartment, $Q$ inter-compartmental clearance, $V_p$ peripheral volume of distribution

[a] 0.45 × age/65

[b] 0.75 for females

[c] 0.71 for females

[d] 0.13 for durations of infusion <70 min

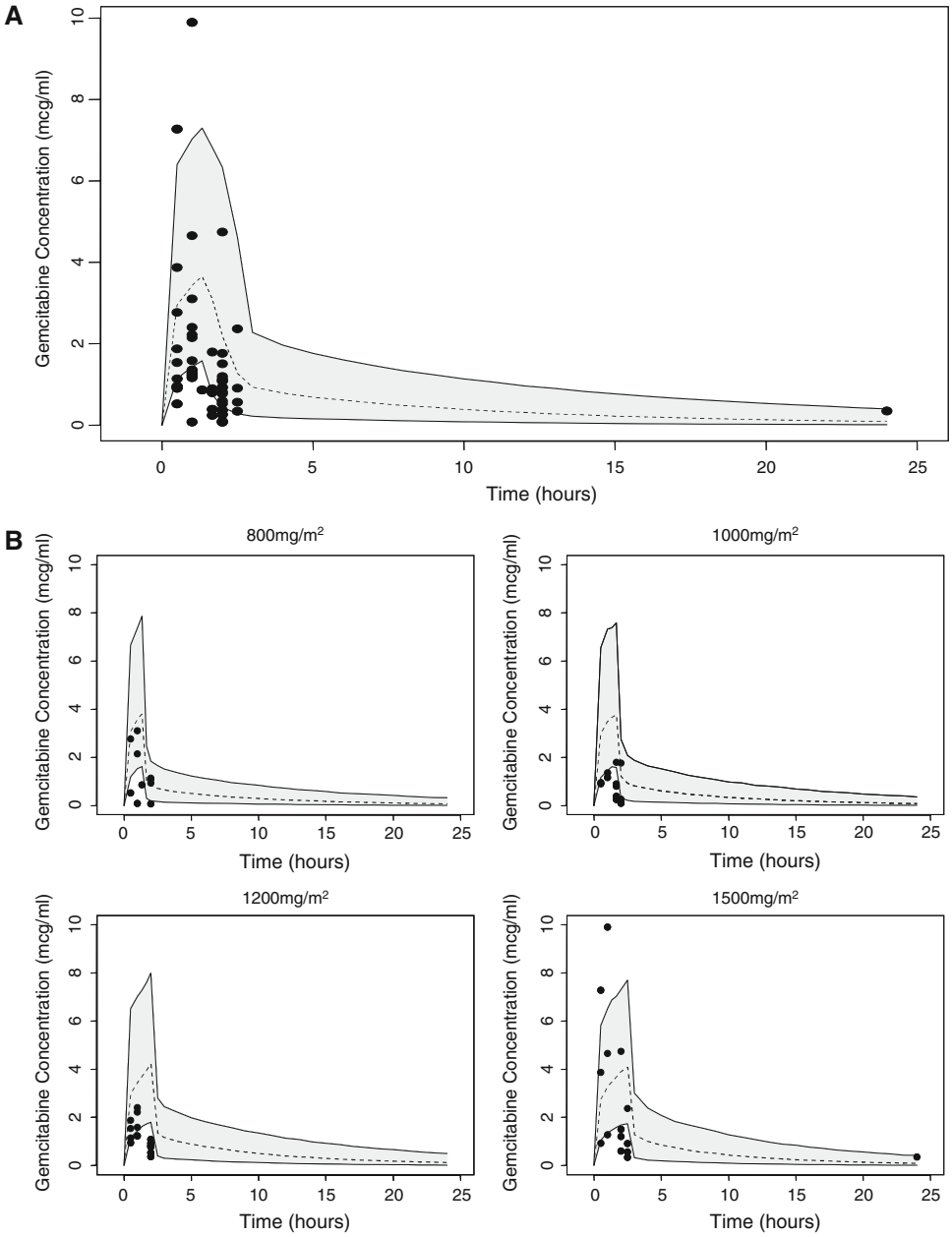


**Fig. 1** Observed and predicted plasma concentrations of gemcitabine for all (**a**) and individual (**b**) dose groups in the dose-escalation phase. The shaded area represents the 10th to 90th prediction interval for gemcitabine concentrations using population PK parameters. The *dotted line* represents the 50th prediction interval (median). The *solid dots* represent the observed data

dose-rate as that of subsequent HAI gemcitabine. To avoid untoward toxicity from a prolonged systemic infusion, patients received IV gemcitabine for an attenuated course (60 min); as a result, formal analysis of PK parameters was not possible. However, since both HAI and IV gemcitabine were given at the same dose-rate, the ratio of plasma drug concentration achieved after HAI to that after IV at a given time point during treatment (e.g., 1 h) provides an estimate of the extent of hepatic extraction of the drug. PK samples collected during both IV and HAI administration were available from 11 patients treated in the IDE (Table 6).

The ratio of gemcitabine levels of HAI to IV at 1 h was highly variable among patients, ranging from 0.09 to 11 (median 0.95). Five patients had an HAI/IV drug ratio of <0.7, indicating hepatic extraction of gemcitabine. The full concentration-time curves of three representative patients demonstrating hepatic extraction of gemcitabine treated in cohort IDE-1 are shown in Fig. 2. However, in three patients, gemcitabine levels obtained after HAI were substantially higher than those achieved following IV treatment (fourfold to 11-fold). Overall, there were no statistical differences between drug levels achieved after IV and HAI ($P = 0.52$ by paired Wilcoxon test). The extent of extraction does not seem to increase with duration of drug infusion. Furthermore, there is no obvious correlation between hepatic extraction of gemcitabine and incidence of myelosuppression or treatment response.

**Table 6** Plasma gemcitabine concentration at 1 h following HAI or IV administration

| Patient | Dose-rate [mg/(m$^2$ min)] | $Conc_{iv}$ (μg/ml) | $Conc_{HAI}$ (μg/ml) | Ratio (HAI/IV) |
|---|---|---|---|---|
| 1 | 5 | 1.73 | 0.45 | 0.26 |
| 2 | 5 | 3.09 | 0.28 | 0.91 |
| 3 | 5 | 2.03 | 0.88 | 0.43 |
| 4 | 5 | 0.18 | 1.95 | 11 |
| 5 | 5 | 0.09 | 0.39 | 4.3 |
| 6 | 3.3 | 0.28 | 0.34 | 1.2 |
| 7 | 3.3 | 1.34 | 6.53 | 4.9 |
| 8 | 3.3 | 4.66 | 3.29 | 0.70 |
| 9 | 2.5 | 3.67 | 1.83 | 0.50 |
| 10 | 2.5 | 3.56 | 3.54 | 0.99 |
| 11 | 2.5 | 2.05 | 1.94 | 0.95 |
| | | | | Median = 0.95 |

*Conc* concentration, *HAI* hepatic arterial infusion, *IV* intravenous

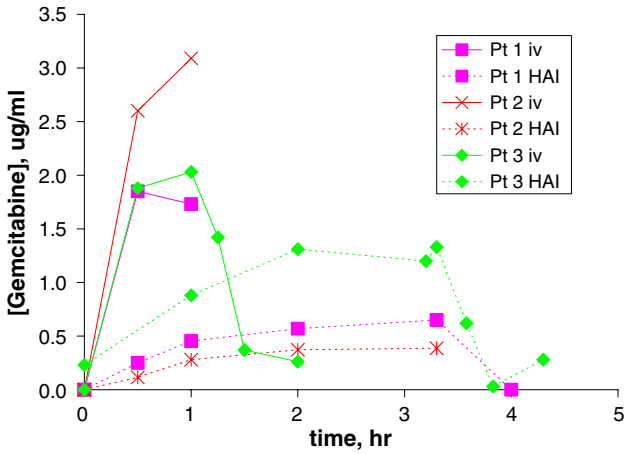


**Fig. 2** Time versus plasma concentration curves of gemcitabine in three representative patients following intravenous (*IV*) and hepatic arterial infusion (*HAI*) treatment who showed hepatic extraction of gemcitabine

### Antitumor activity and disease progression

One patient with cholangiocarcinoma who previously underwent a hepatic resection and received systemic gemcitabine in the adjuvant setting had a partial response in a recurrent solitary hepatic lesion adjacent to the middle hepatic vein. After receiving treatment for 6 months, sufficient tumor shrinkage allowed the patient to undergo a radiofrequency ablation of the hepatic lesion. After the procedure, the patient continued on study for three additional months prior to developing new liver metastases. Eight patients (3 in DE and 5 in IDE phase) had stable disease as the best response, with a median treatment duration of 4.3 months. Of 26 patients who developed disease progression, 18 (69%) had progression in the liver alone, 7 had both intra- and extrahepatic progression, and only 1 patient experienced extrahepatic alone progression.

## Discussion

Hepatic arterial infusion of chemotherapy represents a viable treatment option for patients with metastatic colorectal cancer and primary liver cancers whose diseases are not amenable to surgical resection but remain confined to the liver. Unlike other locoregional therapies, HAI chemotherapy is not limited by tumor size, number, and/or proximity to major vasculatures, all of which are common contraindications to resection and/or ablation. Regional chemotherapy of FUDR via an implantable pump has been extensively studied in patients with liver metastases from colorectal cancer [17, 18, 28].

We have recently completed a phase II study of HAI FUDR for patients with unresectable primary liver cancers [14]. The response rate, median time to progression, and overall survival were encouraging. Sixteen of 34 evaluable patients (47%) had a partial response (15 of 26 with cholangiocarcinoma and 2 of 8 with hepatocellular carcinoma). The median time to progression was 7.4 months and overall survival 29.5 months. Dose reductions for liver function abnormalities were relatively common (median = 1 per patient); the FUDR dose at the end of treatment was 62.5% lower than the starting dose. Of note, 55% of patients who developed disease progression on study continued to have liver-confined disease, indicating that further HAI-based regimens, especially those with less hepatotoxicity, are worth exploring [14].

Gemcitabine appears to be an attractive agent for HAI therapy because of its favorable toxicity profile and proven effectiveness in primary liver cancers. In theory, HAI gemcitabine may provide significant "regional advantage" over systemic administration because of high systemic clearance and possibly high hepatic extraction of the drug [1, 24].

In the DE phase of this study, HAI gemcitabine was given at a fixed dose-rate in order to maximize intracellular accumulation of gemcitabine triphosphates in tumors [6]. In the initial phase I study of fixed dose-rate gemcitabine, escalating doses at 1,000, 1,200, and 1,500 mg/m$^2$ were evaluated. Grade 3/4 leucopenia, neutropenia, and thrombocytopenia were 30.8, 57.7, and 26.9%, respectively [6]. This contrasts with the current HAI study in which a lower incidence of grade 3/4 leucopenia, neutropenia, and thrombocytopenia were observed in the DE phase (6.3, 0, and 12.5%, respectively). Accordingly, gemcitabine dose could be escalated to 1,500 mg/m$^2$ without any protocol-defined DLTs. Comparing with simulated gemcitabine concentrations obtained using population PK parameters, plasma drug levels determined following HAI in the DE phase

were generally lower, suggesting hepatic extraction of the drug.

One major advantage of using FUDR for HAI therapy is that >95% of the drug is extracted by the liver, resulting in little or no systemic toxicity. In the current study, hepatic extraction of gemcitabine was inferred from a comparison between drug levels obtained after IV and HAI administration given at the same dose-rate in the same patient, rather than assessed directly using invasive technique that involved hepatic arterial and venous samplings. Our PK data indicates that a much lower proportion of gemcitabine is extracted and, when occurs, is found only in a sub-set of patients. The reason for the high variability of hepatic extraction is unknown. It may be related to differences in arteriovenous shunting through tumor sinusoids, genetic polymorphisms of nucleoside transporters and metabolizing enzymes among patients, and possibly errors in PK samplings. We initially hypothesized that a more prolonged HAI gemcitabine might improve regional advantage by avoiding saturation of hepatic extraction. Surprisingly, this did not seem to be the case. There was no obvious trend toward increasing hepatic extraction when HAI duration was lengthened from 200 to 400 min. It is unclear whether a more prolonged infusion of gemcitabine given at an even lower dose-rate (e.g., >4 h) will improve hepatic extraction. Such an approach will likely require drug delivery via the constant flow system, rather than the implantable pump. Further drug stability and compatibility testings will be necessary prior to clinical evaluation.

We observed a relatively higher incidence of myelosuppression when a prolonged HAI infusion was given in the IDE phase, with grade 3/4 leucopenia, neutropenia, and thrombocytopenia occurring at 41.7, 16.7, and 16.7%, respectively. An increase in systemic toxicity with prolonged IV gemcitabine infusion has been well documented in the literature. Thus, the MTD of gemcitabine when given as a 24-h infusion to patients with untreated non-small-cell lung cancer was 180 mg/m$^2$, with neutropenia and lethargy being dose-limiting[4]. This contrasts with an MTD of 800–1,250 mg/m$^2$ using a commonly employed, 30-min infusion of gemcitabine. In a phase I study, Pollera et al. [23] evaluated the infusion length-effect relationships of IV gemcitabine given at 300 and 875 mg/m$^2$ over increasing duration of infusion starting at 60 min. The maximum-tolerated infusion time reached after four escalation steps for 300 mg/m$^2$ gemcitabine was 6 hours, with leucopenia being dose-limiting. For the higher dose of 875 mg/m$^2$, infusion duration could not be escalation beyond 60 min due to leucopenia.

Evaluation of liver function abnormalities has proven to be challenging in this patient population, as many have elevations of liver enzymes at baseline and upon disease progression. Hepatic toxicities observed with HAI gemcitabine were mild and manageable when applying a similar dose-modification strategy previously used for managing liver enzyme abnormalities associated with HAI FUDR. The incidence of grade $\geq 3$ AST, Alk Phos, and total bilirubin was 7.1, 7.1, and 3.6%, respectively; no patient required a treatment hold for more than 14 days because of hepatic toxicity, or developed a biliary stricture. The hepatic safety profile of HAI gemcitabine is even more noteworthy, as dexamethasone, a hepatobiliary protective agent commonly given with HAI FUDR, was not used in this study.

In this heavily pretreated population, we observed a partial response in a patient with cholangiocarcinoma who had received systemic gemcitabine in the adjuvant setting. Eight patients had stable disease as the best response. This included a patient with unresectable cholangiocarcinoma refractory to IV gemcitabine who received HAI treatment for more than 7 months prior to removal from study because of pump catheter malfunction. Of note, the majority of first disease progression (69%) occurred in the liver alone, highlighting the potential for further liver-directed treatment in this selected patient population.

Vogl et al. [30] reported a phase I study of HAI gemcitabine with or without microspheres administered in patients with intra-hepatic cholangiocarcinoma or metastases from pancreatic cancer. Gemcitabine was given via a percutaneously placed catheter over $\leq$20 min. The MTD of gemcitabine without or with microspheres was determined to be 1,400, and 1,800 mg/m$^2$, respectively. It is important to note that the MTD of this study was defined as the dose in which two or more patients of one dose group had a WHO grade 3 or 4 myelosuppression or non-hematologic toxicity during cycle 1. Since our current protocol allowed for dose reductions in the presence of grade 3 myelosuppression (leucopenia, neutropenia, and thrombocytopenia), it may be difficult to compare tolerability directly between the two studies.

The current phase I trial paves the way for future combination studies in which HAI gemcitabine can be used in conjunction with high-dose conformal radiotherapy [5] or DNA damage response modulators (e.g., Chk1 kinase inhibitor) [29] to maximize tumor cell kill in the liver.

In summary, this phase I study demonstrates that HAI gemcitabine can be delivered safely to patients via the side port of an implantable pump. The MTD has not been formally reached. When given at a fixed dose-rate of 10 mg/(m$^2$ min), treatment is tolerable up to 1,500 mg/m$^2$. Although dose delays and modifications were not infrequent, a total cumulative dose of 3,975 mg/m$^2$ can be given in the first 4 weeks of treatment. When administrated at 1,000 mg/m$^2$ over a more prolonged period, HAI gemcitabine was tolerable up to 400 min. However, hepatic extraction of gemcitabine seems moderate, and does not improve with a more prolonged infusion. For future studies, we

therefore recommend a starting dose of 1,500 mg/(m$^2$ min) at a fixed dose-rate of 10 mg/(m$^2$ min).

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**Conflict of interest statement** None

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