Cancer Chemother Pharmacol (2007) 60:871–882
DOI 10.1007/s00280-007-0434-7

ORIGINAL ARTICLE

A phase I study of bi-weekly administration of 24-h gemcitabine followed by 24-h irinotecan in patients with solid tumors

Muhammad Wasif Saif · Sandra Sellers · Mao Li · Wei Wang · Linda Cusimano · Hui Wang · Ruiwen Zhang

Received: 10 October 2006 / Accepted: 1 February 2007 / Published online: 8 March 2007

Abstract
Purpose To determine the maximal tolerated doses (MTD) and dose-limiting toxicities (DLT) of combination of 24-h infusions of gemcitabine and irinotecan in patients with advanced solid tumors.
Patients and methods Twenty-four patients with advanced solid tumors received gemcitabine as a 24-h IV infusion followed by a 24-h infusion of irinotecan every 2 weeks. Pharmacokinetic parameters of both drugs and their metabolites were estimated by using non-compartmental methods.
Results Twenty-four patients were fully evaluable for toxicity. DLT was observed in two of six patients at irinotecan/gemcitabine 110/150 mg/m^2 (grade 3 diarrhea and grade 3 GI bleeding). No patient developed acute cholinergic symptoms at any dose. Other toxicities were ≤grade 2 nausea, vomiting, and fatigue. Tumor responses were observed in three patients (one CR: cholangiocarcinoma; two PR: SCLC, gastric neuroendocrine tumor). Stable disease >3 months was found in six patients including five patients who had failed short infusions of either drug. Pharmacokinetic analysis showed that C_{max} of each drug and active metabolites were dose-dependent. High dose of gemcitabine increased C_{max}, AUC, and $T_{1/2}$ of irinotecan. However, gemcitabine had minimal effects on SN-38.
Conclusions The recommended dose for Phase II studies is gemcitabine 125 mg/m^2 given as a 24-h IV infusion on D1 and D15, followed by a 24-h IV infusion of irinotecan 110 mg/m^2 on D2 and D16. Both pretreated patients and chemo-naive patients seem to tolerate higher doses of this combination without significant toxicities. Objective responses among patients with solid tumors, in particular cholangiocarcinoma and small cell lung cancer merits further investigation.

Keywords Gemcitabine · Irinotecan · Colon cancer · Cholangiocarcinoma · Gastrointestinal bleeding · SN-38 · Fixed dose rate infusion · Pancreatic cancer · Small cell lung cancer

This study was approved and funded by the National Comprehensive Cancer Network (NCCN) from general research support provided by Pfizer, Inc.

M. W. Saif · S. Sellers · L. Cusimano
Department of Medicine,
Section of Hematology-Oncology,
University of Alabama at Birmingham (UAB),
Birmingham, AL, USA

M. W. Saif · M. Li · W. Wang · H. Wang · R. Zhang
Department of Medicine,
Department of Clinical Pharmacology and Toxicology,
University of Alabama at Birmingham (UAB),
Birmingham, AL, USA

M. W. Saif (✉)
Section of Medical Oncology,
Yale University School of Medicine,
333 Cedar Street, FMP: 116, New Haven,
CT 06520, USA
e-mail: wasif.saif@yale.edu

Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine, dFdC) is a pyrimidine analog of deoxycytidine, with a broad spectrum of anti-tumor activity against both leukemia and solid tumors including pancreatic, lung, ovarian, hepatobiliary, breast, and colon cancers [1]. Irinotecan is a topoisomerase I-interacting agent with activity in cancers

arising in the gastrointestinal tract, breast, lung, and ovary [2]. Differences in mechanism of action of gemcitabine and irinotecan, combined with the demonstrated anti-tumor activity of each agent, suggest that co-administration of gemcitabine and irinotecan to patients with various solid tumors may provide clinical outcomes superior to those obtained with either drug administered alone. With the exception of myelosuppression, the two drugs have no overlapping toxicity, so that their combination should be feasible. In addition, the results of preclinical studies on MCF-7 breast cancer and the SCOG small cell lung cancer (SCLC) cell lines revealed that the combination of these drugs exerted synergy over a wide range of concentrations on isobologram analysis [3]. In addition to the preclinical studies, Phase I and II studies have also supported the potential clinical value of an irinotecan/gemcitabine combination when used as 60- and 30-min infusions, respectively [4, 5].

Gemcitabine is followed by irinotecan in the clinical trials on the basis of the theoretical rationale that this sequence would afford optimum intracellular concentrations of dFdCTP (gemcitabine-triphosphate) during the interval of maximum DNA strand breakage induced by inhibition of topoisomerase-I by irinotecan [6]. Preliminary results of pharmacokinetic studies assessing levels of gemcitabine, the uridine metabolite of gemcitabine, irinotecan, SN-38, and SN-38G did not show pharmacokinetic differences between the two administration sequences. There was no clear evidence of a superior drug sequence, although patients who achieved long-term stable disease and response had received gemcitabine first followed by irinotecan.

The anti-tumor activity of gemcitabine is not dose-response related but schedule-dependent [7, 8]. In vitro and in vivo studies with various tumor models, including human pancreatic cancer cell lines, demonstrated a superior anti-proliferative activity of gemcitabine in case of prolonged drug exposure [7, 8]. Gemcitabine enters cells by the facilitated nucleoside transport mechanism, and undergoes phosphorylation to the 5′-monophosphate form (dFdCMP) by deoxycytidine kinase (dCK) (Fig. 1). The drug is subsequently phosphorylated by nucleotide monophosphate kinase and nucleotide diphosphate kinase to the 5′-diphosphate (dFdCDP) and 5′-triphosphate derivatives (dFdCTP), respectively. dFdCDP is an inhibitor of ribonucleotide reductase, resulting in decreases in the four physiologic deoxyribonucleotide triphosphates: dATP, dCTP, dGTP, and dTTP. dFdCTP is incorporated into DNA by DNA polymerase, and results in inhibition of DNA synthesis [9]. The phosphorylation of gemcitabine in tumor cells is a saturable process [9]. dCK enzyme is saturated at plasma concentrations achieved after an

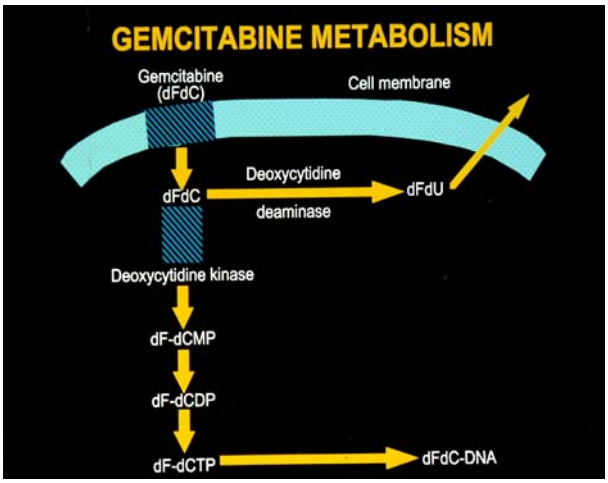

Fig. 1 Metabolism of gemcitabine. Gemcitabine is phosphorylated by deoxycytidine kinase into the active metabolite gemcitabine triphosphate (dF-dCTP). The rate-limiting step in the formation of dF-dCTP is the phosphorylation of gemcitabine to the monophosphate by deoxycytidine kinase. The diphosphate is a potent inhibitor of ribonucleotide reductase, an action that reduces deoxynucleotide pools. Decreased cellular concentrations of deoxycytidine triphosphates permit a more rapid phosphorylation of gemcitabine and decrease the metabolic clearance of gemcitabine nucleotides. As a consequence of this, the active nucleotide forms of gemcitabine are effectively accumulated to high concentrations in the cell

infusion over 30 min. Therefore, accumulation of higher intracellular dFdCTP concentrations, which may result in an enhanced anti-tumor activity, cannot be achieved by higher dosage, but only by prolonged infusion time [10]. There is also evidence that gemcitabine acts as a substrate inhibitor of dCK at high concentrations, which may be the basis for a demonstrable decline in the ability of cells to accumulate dFdCTP at gemcitabine concentrations greater than 20 μmol/l [11, 12].

Based on the preclinical and phase I study, Tempero et al. [13] found improved activity of gemcitabine 1,500 mg/m^2 as a fixed dose rate infusion of 10 mg/m^2/min in comparison to high dose gemcitabine (2,200 mg/m^2) infusion over 30 min in pancreatic cancer. Pharmacokinetic analysis in this study also revealed significantly higher concentrations of intracellular dFdCTP with the prolonged infusion. However, grade 3–4 hematologic toxicity occurred in up to almost 50% in the fixed dose rate arm. In contrast, in other trials using a 24-h gemcitabine at a dose of 100 mg/m^2 hematologic toxicity was mild [14]. Therefore, we chose 24-h gemcitabine infusion so that it can be safely combined with irinotecan.

There are several rationales for testing prolonged continuous infusions of irinotecan. Experimental data suggests that the cytotoxicity of camptothecin is highly dependent on ongoing DNA replication and on the

fraction of cells in S-phase [15]. The clinical implication of these findings is that longer drug exposures may produce greater anticancer effects [16]. Furthermore, high drug concentrations may not be necessary to cause a clinically significant amount of DNA damage. Rather, maintaining prolonged steady-state SN-38 lactone levels above a low but critical threshold concentration may be a more crucial determinant for eventual cell lethality. In vivo animal studies support the concept that protracted low dose exposures to camptothecins produces excellent anti-tumor activity, and less host toxicity. Because the parent compound must be enzymatically activated to the metabolite, SN-38, potential saturation of the activating enzyme may occur following drug administration as a short IV infusion [17]. In contrast, a prolonged infusion of irinotecan may avoid high saturating plasma levels, and may result in a relatively greater percent conversion of drug to the active metabolite [18]. There is evidence that patients with severe diarrhea also have a decreased capacity to glucuronidate SN-38, resulting in high biliary concentrations of unconjugated SN-38 [19]. Saturation of glucuronidation leads to higher drug concentrations of unconjugated SN-38. Data from a prior phase I trial (NCI) of irinotecan given as a 96-h infusion weekly for 2 of 3 weeks confirmed that the molar ratio of SN-38 to CPT-11 was about sixfold higher than reported with short infusion schedules; further, the incidence of severe diarrhea was quite low compared to that seen with the typical 60–90 min infusions [15].

Based on the above rationale, we performed a Phase I study to determine the maximal tolerated dose (MTD), dose limiting toxicities (DLTs) and pharmacokinetic analysis of gemcitabine and irinotecan on a novel schedule: gemcitabine (24-h infusion) day 1, day 15 and irinotecan (24-h infusion) day 2, day 16 on a biweekly schedule.

Patients and methods

Patient selection

Patients with histologically confirmed advanced solid tumors that had failed to respond to standard therapy or for which no standard therapy was available were eligible to participate in this study. Other eligibility criteria included measurable or assessable disease by computed tomography; age at least 19 years; ECOG performance status of $\leq$2; absolute neutrophil count (ANC) of at least 1,500/μl; platelet count of at least 100,000/μl; serum creatinine level less than 1.3 mg/dl; total bilirubin less than 1.0 mg/dl; and AST and ALT levels less than 2.5 times the upper limit of normal; and >4 weeks since any prior therapy and recovery from any side effects. Prior therapy with irinotecan (60–90 min) or gemcitabine (30 min) given as a short-infusion was allowed. All patients gave written informed consent according to federal and institutional guidelines.

Study design

This was an open label, single center, non-randomized, dose-escalating phase I study. The patients received gemcitabine as a 24-h IV infusion on days 1 and 15 followed by irinotecan as a 24-h IV infusion on days 2 and 16 of each 4-week cycle, administered in the in-patient GCRC. Four weeks constitute one complete cycle.

Dose-escalation and definition of study endpoints

The starting dose for irinotecan, 70 mg/m^2 was 50% of the recommended phase II dose (140 mg/m^2) when given as a 24-h infusion every 2 weeks with oral UFT [20]. The starting dose of gemcitabine, 75 mg/m^2, was 50% of the recommended phase II dose (150 mg/m^2) when given as a 24-h infusion with cyclophosphamide [21]. As mentioned earlier, we chose a 24-h gemcitabine schedule due to milder hematologic toxicity in contrast to fixed dose rate schedule of gemcitabine [13, 14], so that it can be safely combined with irinotecan. Initially, the dose of irinotecan was escalated from 70 mg/m^2 $\rightarrow$ 90 mg/m^2 $\rightarrow$ 110 mg/m^2 with a fixed dose of gemcitabine (75 mg/m^2) (Table 1). Cohorts of 3–6 patients were entered at each dose level until DLT is seen and the MTD was established or a maximum irinotecan dose of 110 mg/m^2. After reaching irinotecan at 110 mg/m^2, gemcitabine was escalated from 75 mg/m^2 $\rightarrow$ 100 mg/m^2 $\rightarrow$ 125 mg/m^2 $\rightarrow$ 150 mg/m^2 in similar fashion. If no DLT is observed at irinotecan 110 mg/m^2 and gemcitabine 150 mg/m^2, then the dose of irinotecan may be escalated to 140 mg/m^2, the previously recommended dose for phase II study (Table 1). Before entry of patients at a new dose level, all patients at the previous dose level must have been observed for at least 4 weeks. No intra-patient dosage escalation was permitted.

For purposes of determining the MTD, only DLT's occurring during the first cycle of therapy were considered. Dose-limiting toxicities were defined as any of the following: grade 4 neutropenia lasting at least 5 days; grade 3 or 4 neutropenia associated with fever $\geq$38.5°C; grade 4 thrombocytopenia lasting at least 5 days; grade 3 or 4 non-hematologic toxicity excluding alopecia; or the need for a treatment delay of more than 2 weeks to permit resolution of toxicity. If one or more patients at a dose level experienced DLT then three additional

Table 1 Study design and dose escalation schema

Dose level	Repeat q 4 weeks (1 cycle = 4 weeks)	
	Gemcitabine 75 mg/m^2 24-h CIV D 1, 15	Irinotecan 24-h CIV D 2, 16
	Fixed dose	Irinotecan dose escalation
Part 1		
1	75 mg/m^2/24 h	70 mg/m^2
2	75 mg/m^2/24 h	90 mg/m^2
3	75 mg/m^2/24 h	110 mg/m^2
	Gemcitabine dose escalation	Fixed dose of irinotecan
Part 2		
4	100 mg/m^2/24 h	Determined from part 1
5	125 mg/m^2/24 h	Determined from part 1
6	150 mg/m^2/24 h	Determined from part 1
7	150 mg/m^2/24 h	140 mg/m^2/24 h

patients were treated at that dose level. The MTD was defined as the dose below at which two of the first three patients per cohort or ≥2 of six patients experience DLT (related to therapy). Patients who experienced DLT could be continued on treatment at a modified dose at the discretion of the treating physician if they appeared to be benefiting from the therapy.

Gemcitabine and irinotecan were commercially available and were prepared for administration according to directions in the package labeling. Patients received 10 mg dexamethasone and 24 mg ondansetron IV/PO 30 min prior to the start of irinotecan.

Dose modifications

Dose reductions in individual patients during the treatment cycle

When a DLT occurred during the first cycle of the study, treatment with chemotherapy was interrupted until the toxicity resolves to ≤grade 1. Treatment was then be reinstituted at the previous dose level. Treatment was then being re-instituted using the appropriate reductions as described below. A 25% reduction in the gemcitabine dose was considered for hematologic toxicity or non-hematologic toxicity felt to be aggravated by gemcitabine such as skin rash, asthenia, headache, or other toxicities in the judgment of the principal investigator. Similar guidelines were applied to irinotecan. Dose adjustments on day 15 were made following the guidelines shown below based on absolute neutrophil count (ANC) and platelet counts, taken on the day of therapy, and clinical assessment of non-hematologic toxicities.

During a cycle

The second treatment of each cycle should begin on day 15 (day 1 = the start of the cycle) provided his CBC with differential drawn on Day 15 are: ANC ≥ 1,500/μl, platelet count is ≥100,000/μl, and all clinically significant non-hematologic toxicities have resolved. The day 15/16 dose of gemcitabine and irinotecan will be modified based according to the same guidelines in Tables 2 and 3 and dose levels outlined in Table 1.

Criteria for starting the next cycle

If no interruptions occurred, the next treatment cycle should begin on day 29 (day 1 = the start of the preceding cycle) provided: ANC > 1,500/μl, platelet count is >100,000/μl, and all clinically significant non-hematologic toxicities have resolved (Tables 2, 3). If the ANC and platelet counts were below 1,500 and 100,000/μl on day 29, the treatment was delayed for 1 week and later treated according to Table 2. A subject who required longer than 3 weeks for resolution of toxicity were considered off study. If the prior treatment cycle was interrupted for toxicity prior to administering all of the

Table 2 Dose modifications for hematologic toxicity

Granulocyte nadir: prior cycle (per μl)	Platelet nadir: prior cycle (× 1,000/μl)	Full doses mid-cycle?	Dose of Irinotecan or Gemcitabine for next cycle
≥1,000	≥75	Yes	Increase to next level provided there was no treatment delay
		No	Continue at same dose level
501–999 or	50–74.9	Yes	Decrease 1 dose level
		No	Decrease 1 dose level
≤500 or	≤49	Yes	Decrease 1 dose level
		no	decrease 2 dose levels
Treatment delay required			
Day 36: <1,500 or	<100		Delay 1 more week
Day 36–42: 1,000–1,499 or	50–74.9		Resume, but decrease 1 dose level
Day 50: <1,000 or	<49		Discontinue

Table 3 Dose modifications for nonhematologic toxicity

Toxicity grade: prior cycle	Full doses given mid-cycle?	Dose of irinotecan or gemcitabine for next cycle
0–1	Yes	Increase to next level provided there was no treatment delay
	No	Continue at same dose
2	Yes	Continue at same dose level
	No	Decrease 1 dose level
≥grade 3 at any time		Decrease one dose level
Treatment delay required		
day 36: ≥grade 1		Delay 1 more week
day 42: ≤grade 1		Resume, but decrease one dose level
day 50: ≥grade 2		Discontinue

intended therapy, the cycle could begin no sooner than 14 days after the last treatment provided the ANC is >1,500/μl, the platelet count is >75,000/μl, and all clinically significant non-hematologic toxicities have resolved.

During the portion of the trial in which irinotecan dose escalation was proceeding, the dose of irinotecan was preferentially decreased and dose of gemcitabine was kept the same and vice versa for gemcitabine dose escalation period. If multiple toxicities were observed in the preceding cycle, the dose administered was based on the most severe toxicity experienced. Patients who required a dose reduction of either irinotecan or gemcitabine for toxicity remained at the reduced dose of that drug.

Pretreatment and follow-up studies

All laboratory and radiological tests as well as history and physical examination required assessing eligibility had to be completed within 7 days prior to start of treatment. Assessment of toxicity and hematology tests were performed weekly during each cycle of therapy. Tumor assessments were performed after every two cycles of therapy and response was assessed using RECIST criteria [22].

Pharmacokinetic methodology

Clinical pharmacokinetic studies of gemcitabine and irinotecan were performed on cycle 1 for each patient. For pharmacokinetic studies, blood samples (5 ml for gemcitabine treated group, 10 ml for irinotecan treated group) were collected before administration, at 1, 4, 8, and 23 h after the start of the infusion, and at 0.08, 0.5, 1, 2, 4, 8, and 24 h after the end of the infusion. Blood was placed into heparinized tubes (for gemcitabine treated group, containing 5u CDIT), centrifuged at 2,000*g* for 5 min, and the resulting plasma was decanted into a separate tube and stored at −70°C until analyzed.

High-pressure liquid chromatography analysis

Gemcitabine (dFdC) and its metabolite 2dFdU (2′, 2′-Difluorodeoxyuridine)

Gemcitabine was analyzed using the following procedures. Plasma (480 μl) was mixed with 24 μl of 20 μg/ml 2′-deoxycytidine and 960 μl of acetonitrile, vortexed for 10 s, and then centrifuged at 14,000 rpm for 10 min. The entire supernatant was transferred into a new 10 × 75 glass tube and evaporated to dryness using a steady stream of dried air at room temperature. The residue was reconstituted into 120 μl ddH_2O. An aliquot of 100 μl was injected into the HPLC column. Gemcitabine (dFdC) and its metabolite 2dFdU were analyzed by a modification of previously reported HPLC methods [23, 24]. The HPLC system was composed of a Beckman Gold module 406 (Beckman Coulter, Fullerton, CA, USA) with computer-controlled 126 solvent delivery system and 168 UV detector. Determination of Gemcitabine was achieved using a Zorbax SB-C18 (5 μm, 150 × 4.6 mm) analytical with a LiChroCART 100 RP-18 guard column. The flow rate was 1.6 ml/min. The column elute was monitored by UV at 275 nm. The mobile phase was composed of 0.5 M ammonium acetate, pH 6.8 (A) and 50% methanol in ddH_2O (B). A linear gradient start at 100% A and go to 60% B over 30 min. Prior to application, the mobile phase is filtered and degassed using a Millipore glass filter system with a nylon membrane (0.2 μm). The retention times were 5.8 min for gemcitabine, 7.8 min for its metabolite 2dFdU. Peak height was determined for quantification of Gemcitabine and 2′,2′-difluorodeoxyuridine. Linear regression and correlation analysis were carried out to establish the standard

peak-height/concentration curves for gemcitabine and 2′,2′-dfluorodeoxyuridine.

Irinotecan and SN-38

Irinotecan was analyzed using the following procedures. Plasma (700 µl) was mixed with 700 µl of ice-cold methanol–acetonitrile mixture (50:50; V:V), vortexed for 10 s, and then centrifuged at 14,000 rpm for 10 min. A 1,000 µl of supernatant was transferred into a new 10 × 75 glass tube and evaporated to dryness using a steady stream of dried air at room temperature. The residue was reconstituted into 200 µl of mobile phase and filtered with nylon membrane (0.2 µm). An aliquot of 50 µl was injected into the HPLC column. Lactone and carboxylate forms of irinotecan and SN-38 were analyzed by a modification of previously reported HPLC methods [25–28]. The chromatographic system consisted of an HP 1050 HPLC (Hewlett Packard, Palo Alto, CA) with computer-controlled solvent delivery system and an HP fluorescence detector. A reversed-phased HPLC column ZORBAX SB-C_{18} (150 × 46 mm) was used. The mobile phase consisted of 0.075 M ammonium acetate buffer (pH 6.4)-acetonitrile (78:22; V:V), to which PIC-A solution (15 ml/l) was added. The column was eluted at a flow rate of 1.40 ml/min. Fluorescence detection was carried out at an excitation wavelength of 375 nm and emission wavelengths of 420 nm for the two forms of CPT-11 and of 520 nm for the two forms of SN-38. The retention times were 3.5 min for carboxylate irinotecan, 5.4 min for carboxylate SN-38, 6.5 min for lactone irinotecan, and 10 min for lactone SN-38. Peak area was determined for quantification of two forms of CPT-11 and SN-38. Linear regression and correlation analysis was carried out to establish the standard peak-area/concentration curves for two forms of CPT-11 and SN-38.

Statistical methods

An escalation design with three to six patients was chosen on empiric grounds, according to current standards in phase I cancer trials [29]. The chance of not detecting a toxicity that occurs in fact in every second patient is only 1.6% in a cohort of six patients, and less than 0.1% in a cohort of 12.

Pharmacokinetic parameters were estimated by using WinNonlin programs (Version 4.1, Mountain View, CA, USA). They include the area under the curve (AUC, ng or µg h/ml), initial half-life ($T_{1/2\alpha}$, min), terminal half-life ($T_{1/2\beta}$, min), time to maximum concentration (T_{max}, h), maximum concentration (C_{max}, ng or µg/ml) and Clearance (CL, ml/kg/h). A non-compartment model was used to fit the concentration-time curves.

Results

Patients

Twenty-four patients, whose pertinent characteristics are listed in Table 4, received 89 total courses with the median number of 4 cycles (range 1–8) (Table 5).

Toxicity

DLT

No DLTs were observed when three patients being treated at each dose level of irinotecan 70, 90, and

Table 4 Treated patient demographics (n = 24)

Characteristic	No. of Patients
Patients enrolled	24
Men	20
Women	4
Median age, years (range) 57 (35–85)	-
Race (Caucasian:Black)	22:2
ECOG performance status	
0	0
1	19
2	5
Prior therapy	
Chemotherapy only	18
Chemotherapy and radiation	2
None	4
Diagnosis	
Colorectal	7
Pancreatic	7
Bile duct	2
Neuroendocrine of stomach	1
Renal cell	1
Unknown primary	2
Lung	1
Ovarian	1
Paraganglioma	1
Prostate	1

Table 5 Dose levels, patient enrolled, and number of courses

Dose level	Gemcitabine (mg/m^2/day)	Irinotecan (mg/m^2)	Number of patients	Number of cycles
1	75	70	3	10
2	75	90	3	15
3	75	110	3	30
4	100	110	6	10
5	125	110	3	9
6	150	110	6	15

Table 6 Dose limiting toxicity with the first complete cycle of therapy (days 1,2,15, and 16)

Irinotecan mg/m^2 over 24 h	Gemcitabine mg/m^2 over 24 h	Patients (Evaluate)	Dose-limiting toxicity?
70	75	3	0
90	75	3	0
110	75	3	0
110	100	6	1 Grade 4 Neutropenia
110	125	3	0
110	150	6	2 Grade 3 GI Bleeding → MTD Grade 3 Diarrhea → MTD

110 mg/m^2 with a fixed dose of gemcitabine 75 mg/m^2. One of the six patients treated with gemcitabine 100 mg/m^2 with irinotecan 70 mg/m^2 experienced grade 4 neutropenia (Table 6). No DLTs were observed when three patients treated at gemcitabine 125 mg/m^2 with a fixed dose of irinotecan 110 mg/m^2. Two of the six patients treated at gemcitabine/irinotecan dose of 150/110 mg/m^2 experienced DLTs: grade 3 diarrhea in one and grade 3 gastrointestinal bleeding in another patient [30]. Therefore, based on the DLTs, the MTD was defined as gemcitabine/irinotecan 150/110 mg/m^2. There were four dose modifications due to lowered absolute neutrophil count, including the patients with DLT.

Hematological toxicity

Three patients developed grade 3 neutropenia, which resolved after delaying the therapy, and one patient (DLT) had neutropenic fever (Table 7). Only two patients had grade 3 thrombocytopenia. Interestingly, anemia was the most common hematologic toxicity observed in the study when all the cycles were included. Forty three percent patients were noticed to have grade 2 anemia. Only one patient had grade 3 anemia, which later developed gastrointestinal bleeding (DLT) with grade 4 anemia. All but three anemic patients were treated with erythropoietin without any requirement for blood transfusion. Further analysis of anemic patients revealed that anemia prevalent in patients with those prior multiple chemotherapy regimens (range 1–6), approximately 40% had prior pelvic radiotherapy (Table 8).

Table 7 Hematological toxicity during cycle 1

Dose Level	No. of patients	ANC			Platelets			Anemia			DLT
		2	3	4	2	3	4	2	3	4	–
1	3	–	–	–	–	–	–	1	–	–	–
2	3	–	–	–	–	–	–	3	1	–	–
3	3	–	–	–	–	–	–	2	–	–	–
4	6	–	–	1	–		–	–	–	–	Yes
5	3	–	1	–	–	–	–	2	–	–	–
6	6	–	2	–	–	1	–	3	–	4[a]	Yes

Number of patients with grade of toxicity

Number of patients with DLT

[a] GI bleeding

Non-hematological toxicity

Adverse events according to NCIC CTC 3.0 are presented for the whole patient group (Table 9). No patient developed acute cholinergic symptoms at any dose. Other toxicities were ≤grade 2 nausea, vomiting, elevation of bilirubin or aminotrasferases and fatigue. Only one patient had grade 3 diarrhea (DLT). Except for the observed DLT diarrhea, no clear-cut dose/toxicity relationship was evident.

Anti-tumor activity

Tumor responses were observed in patients with metastatic cholangiocarcinoma (1 complete response), small cell lung cancer (1 partial response), and gastric neuroendocrine tumor (1 partial response). Stable disease

Table 8 Evaluation of anemia during all cycles

Dose level	Grade of anemia	No. of prior chemo	Prior XRT
1	2	4	Yes
2	2	5	Yes
2	2	4	No
2	2	6	No
3	2	4	Yes
3	2	6	No
4	2	None	No
5	2	2	No
5	2	3	Yes
6	4 (GI Bleeding)	1	Yes
6	2	1	No
6	2	None	No
6	2	2	No

Anemia prevalent in those: Prior Chemo: range 1–6; 40% had XRT; G 3 in same pt with G 2 and G 4 in patient with GI bleeding

Table 9 Non-hematologic toxicity during cycle 1

Dose level (mg/m^2)	No. of patients	Number of patients with grade of toxicity															DLT
		Nausea/vomiting			Diarrhea			Fatigue			Edema			Hepatic dysfunction			
		2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	
1	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
2	3	–	–	–	–	–	–	–	–	–	2	–	–	2	–	–	0
3	3	–	–	–	–	–	–	1	–	–	–	–	–	2	–	–	0
4	6	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	0
5	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
6	6	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	1

Number of patients with grade of toxicity

Number of patients with DLT

>3 months was found in six patients including five patients who had failed short infusions of CPT-11 as well as gemcitabine for colorectal and pancreatic cancers, respectively (Tables 10, 11).

Pharmacokinetic analyses

The pharmacokinetic parameters of gemcitabine and irinotecan were estimated in 24 patients at both individual and group levels based on treatment regimens. Significant inter-patient variations in PK of both drugs and metabolites were observed (Table 12; Figs. 2, 3). Pharmacokinetic analyses of irinotecan and SN38 showed that there was no difference in T_{max} at different levels (median: 23.36 ± 0.36), C_{max} was dose-dependent (range: 123.56 ± 0.36 to 373.20 ± 51.43), half life of irinotecan seems to increase with increasing doses of dFdC, AUC_{last} (3291.64 ± 218.16 to 8946.16 ± 1283) and CL (38.65 ± 5.15 to 27.78 ± 3.02) were dependent on the dose of irinotecan. Majority of drug was present in plasma as parent drug (irinotecan), and SN-38 was present less than 5%. There was also no difference in T_{max} for dFdC (median: 26.04 ± 1.96), C_{max} was dose-dependent (1.67 ± 0.1 to 3.92 ± 0.35), high dose of irinotecan seems to increase the half life of dFdU, AUC_{last} was associated with the dFdC dose (54.81 ± 4.67 to 112.65 ± 12.11), majority of the drug present in plasma as 2dFdU, and dFdC (parent drug) was present at all times, although at low concentration. At the same dose level of irinotecan, gemcitabine increased the C_{max} and AUC of irinotecan and decreased its CL, but had minimal effects on the PK of SN-38.

Discussion

The recommended dose for Phase II studies is gemcitabine 125 mg/m^2 given as a 24-h IV infusion on D1 and D15, followed by a 24-h IV infusion of CPT-11 110 mg/m^2 on D2 and D16. PK interactions between gemcitabine and irinotecan were observed, which may have implications in therapeutic effects and side effects of this combination therapy. DLTs that were clearly chemotherapy-related included diarrhea. Overall, the regimen was relatively well tolerated with manageable hematologic and nonhematologic toxicities. The second DLT was gastrointestinal bleeding, which we

Table 10 Summary of best objective responses

Dose level	CR	PR	SD	PD	Not done
1	–	–	1 (Colon)	1	–
2	–	–	–	3	–
3	–	1 (NE)	1(Colon)	1	1[a]
4	1 (Cholangio)	1 (SCL)	1 (CUP) 1(Renal)	1	1[b]
5	–	–	1 (ovarian: MR)	1	1[a]
6	–	–	3 (Pan Ca)	1	–

Note: Both CRC and Pan Ca had prior irinotecan (60-minute) and gemcitabine (30-min)

Patient with small cell lung cancer who achieved a partial response had failed a 60-min infusion of irinotecan given with caboplatin

Cholangio Cholangiocarcinoma, *RCC* renal cell carcinoma, *CRC* colorectal cancer, *CUP* carcinoma of unknown primary, *Pan Ca* pancreatic cancer

[a] Clinical deterioration, [b] DLT

Table 11 Duration of response (CR or PR) and disease control (SD)

Diagnosis	Best response	Duration of response	Reason to stop study drug
Cholangiocarcinoma	CR	8 months (achieved after 4 cycles)	An extra 4 cycles given after CR
Small cell lung cancer	PR	3 months	Palliation of previous bone mets requiring local radiotherapy
Neuroendocrine tumor of stomach	PR	8.5 months	Patient's request
CRC	SD	4 months	Patient requested due to erbitux approval
CRC	SD	4 months	Patient requested due to erbitux approval
Pancreatic cancer	SD	4 months	PD
Pancreatic cancer	SD	4 months	PD
Pancreatic cancer	SD	3 months	Decline in PS
Renal cell carcinoma	SD	6 months	Treated on gemcitabine off study
Carcinoma of unknown primary	SD	4 months	Patient's request to change therapy due to lack of response
Cystadenocarcinoma of ovaries	SD (MR)	6 months	Treated on gemcitabine off study

Both CRC and pancreatic cancer patients had prior irinotecan and gemcitabine

CRC colorectal cancer, *MR* minor response (23% decrease and decline in CA 125), *PD* progressive disease

Table 12 Summary of pharmacokinetic parameters

Parameters	G1/Mean (SE)	G2/Mean (SE)	G3/Mean (SE)	G4/Mean (SE)	G5/Mean (SE)	G6/Mean (SE)
(a) Pharmacokinetic parameters of gemcitabine (dFdc)						
T_{max} (h)	16.53 (7.76)	36.50 (9.39)	23.36 (0.36)	15.50 (5.55)	18.00 (7.00)	9.00 (5.92)
C_{max} (μg/ml)	0.05 (0.03)	0.15 (0.05)	243.27 (25.99)	0.43 (0.16)	0.64 (0.31)	0.08 (0.04)
$T_{1/2}$ (h)	238.3 (0.00)	16.10 (0.00)	6.09 (1.34)	6.50 (1.55)	4.25 (0.00)	10.71 (0.00)
AUC_{last} (μg h/ml)	0.65 (0.54)	1.96 (1.17)	4626.02 (649.16)	1.81 (0.79)	1.85 (0.87)	1.04 (0.71)
CL (ml/h)	7.32 (0.00)	42.67 (0.00)	45.20 (2.88)	127.15 (61.82)	49.02 (0.00)	369.82 (0.00)
(b) Pharmacokinetic parameters of gemcitabine's metabolite 2dFdU						
T_{max} (h)	26.25 (1.75)	24.54 (0.46)	24.22 (0.14)	24.73 (0.85)	9.67 (9.17)	25.60 (1.02)
C_{max} (μg/ml)	1.67 (0.19)	1.82 (0.05)	1.70 (0.07)	2.82 (0.35)	3.27 (0.57)	3.92 (0.35)
$T_{1/2}$ (h)	47.70 (2.08)	46.12 (7.70)	65.38 (21.25)	59.56 (12.89)	139.76 (96.68)	49.20 (11.43)
AUC_{last} (μg h/ml)	54.81 (4.67)	46.50 (3.06)	53.75 (0.79)	21.37 (9.56)	102.96 (16.40)	112.65 (12.11)
CL (ml/h)	1.05 (0.21)	1.29 (0.02)	0.90 (0.14)	0.45 (0.20)	0.92 (0.43)	0.92 (0.28)
(c) Pharmacokinetic parameters of irinotecan						
T_{max} (h)	23.54 (0.54)	23.75 (0.75)	23.36 (0.36)	23.54 (0.54)	40.03 (7.97)	23.86 (0.22)
C_{max} (ng/ml)	123.56 (0.36)	213.21 (15.68)	243.27 (25.99)	123.56 (0.36)	368.35 (74.03)	373.20 (51.43)
$T_{1/2}$ (h)	7.38 (0.76)	6.29 (0.21)	6.09 (1.34)	7.38 (0.76)	2.97 (0.00)	7.25 (0.80)
AUC_{last} (ng h/ml)	3291.64 (218.16)	5269.03 (433.79)	4626.02 (649.16)	3291.64 (218.16)	7125.28 (1740.14)	8946.16 (1283.20)
CL (ml/h)	38.65 (5.15)	33.00 (5.30)	45.20 (2.88)	38.65 (5.15)	16.20 (0.00)	27.78 (3.02)
(d) Pharmacokinetic parameters of SN38						
T_{max} (h)	2.34 (1.67)	18.00 (14.00)	36.00 (6.11)	18.43 (5.32)	5.67 (2.33)	25.60 (6.42)
C_{max} (ng/ml)	24.77 (23.23)	0.70 (0.02)	0.83 (0.11)	0.84 (0.06)	0.69 (0.03)	0.71 (0.02)
$T_{1/2}$ (h)	72.78 (64.78)	–	–	304.12 (0.00)	2142.27 (1351.79)	231.48 (99.54)
AUC_{last} (ng h/ml)	40.69 (10.64)	24.28 (2.03)	28.26 (6.20)	30.03 (1.05)	29.86 (0.70)	29.12 (0.73)
CL (ml/h)	0.48 (0.00)	–	–	462.7 (0.00)	275.70 (184.61)	2445.85 (1168.83)

regarded as the first report of radiation-recall associated with gemcitabine and published elsewhere [30]. Exact etiology of this recall is not known but may be either secondary to altered pharmacodynamics of gemcitabine, lowering of the inflammatory threshold in irradiated tissue, or a result of vascular damage.

Maintaining single-agent doses of chemotherapy drugs when used in combination regimens may be more challenging in advanced stage cancer patients, as they are generally frailer and less tolerant of toxic side effects. This challenge arises particularly in patients who have received multiple chemotherapy regimens in the past. A strategy one might consider to improve the dose intensity of gemcitabine and irinotecan combinations is related to the schedule of administration [31]. Gemcitabine regimens using biweekly regimen instead of the day 1, 8, and 15 every 28-day cycle have been associated with increased dose intensity [32]. It has been shown both in Phase I and Phase II trials that the every 2-week schedule has been better tolerated,

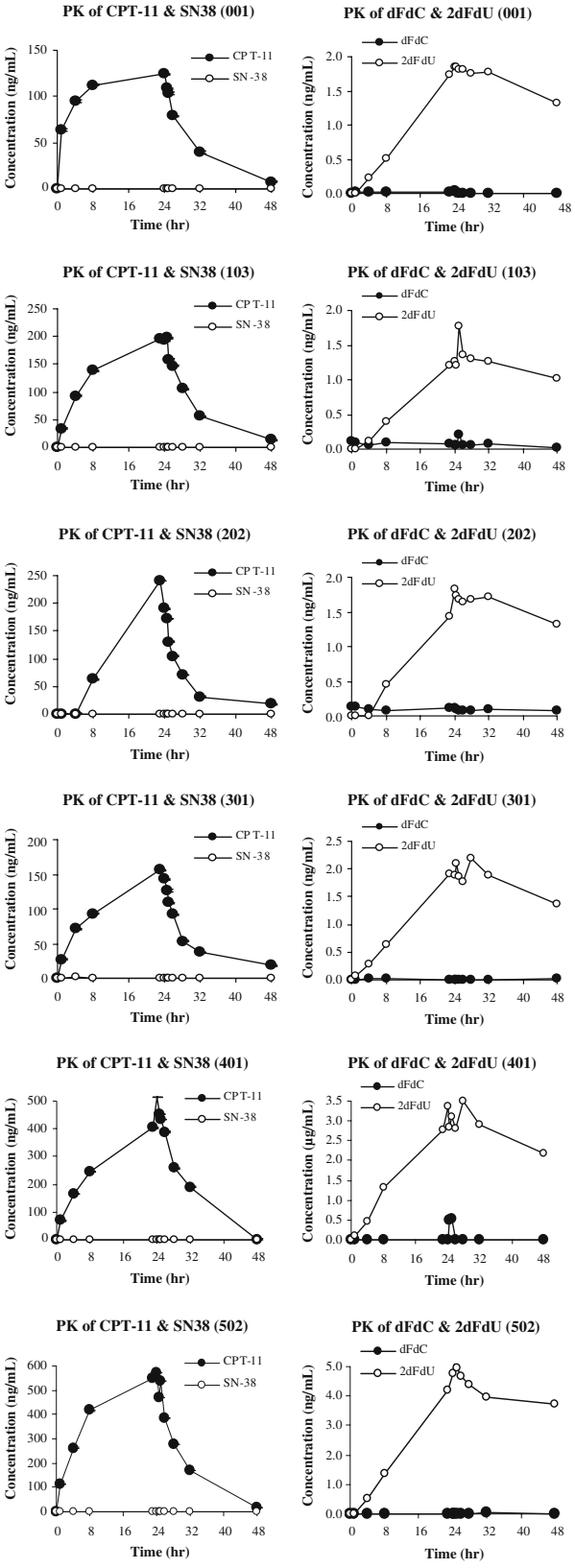

Fig. 2 Pharmacokinetics of irinotecan (CPT-11), SN-38, dFdC (gemcitabine) and dFdU. (Dose level 1: 001; dose level 2: 103; dose level 3: 202; dose level 4: 301; dose level 5: 401; dose level 6: 502)

requiring fewer doses to be withheld. With single-agent irinotecan, a schedule of four weekly doses for an every 6-week cycle is generally associated with more diarrhea during weeks 3 and 4. In a randomized study, the regimen of once every 3 weeks was associated with a significantly lower incidence of severe diarrhea [33]. This finding was similar to our previous study that evaluated 5-FU with 24-h infusion of irinotecan [28]. Therefore, a biweekly regimen also seems feasible.

In this Phase I study, the subject population was heterogenous in terms of histology and prior therapy, and efficacy was not the primary endpoint. However, three responses including a complete response were seen among 24 patients. The patient (metastatic cholangiocarcinoma) who achieved the complete response has no recurrent disease for a year now. Stable disease >3 months was found in six patients including five patients who had failed short infusions of CPT-11 (IFL regimen) for colorectal cancer [34] as well as gemcitabine (30-min) for pancreatic cancer [35]. Treatment in two colorectal patients was stopped upon patients request due to the approval of newer monoclonal antibodies (erbitux) for this disease. Also the patient with small cell lung cancer who achieved a partial response had failed a 60-min infusion of irinotecan given with caboplatin. One patient with cystadenocarcinoma of ovaries had a minor response (23% shrinkage) with a response in CA-125 dropping from 224.6 to 36.1. In summary, the objective response in small cell lung cancer and cholangiocarcinoma and clinical benefit in colon and pancreatic tumors need further investigation.

As mentioned earlier, grade 3–4 hematologic toxicity was observed in approximately 50% of patients who were given fixed dose rate infusion of gemictabine while in a phase II trial of weekly 24-h infusion of gemcitabine in patients with advanced gallbladder and biliary tract, only mild hematologic toxicity was seen. Similarly, in our study, three patients developed grade 3 neutropenia, which resolved after delaying the therapy, and one patient (DLT) had neutropenic fever. The patient with neutropenic fever had been heavily pre-treated with multiple chemotherapy regimens. Decreased neutropenia in this regimen similar to previous findings [14] favors a 24-h infusion over the fixed dose rate infusion of gemcitabine [13].

Only one patient had grade 3 diarrhea and 1 had grade 2 diarrhea. Also, no cholinergic syndrome (early diarrhea, rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping) was observed in any patient. This finding is similar to our previous study in which a modified "FOLFIRI" regimen using a

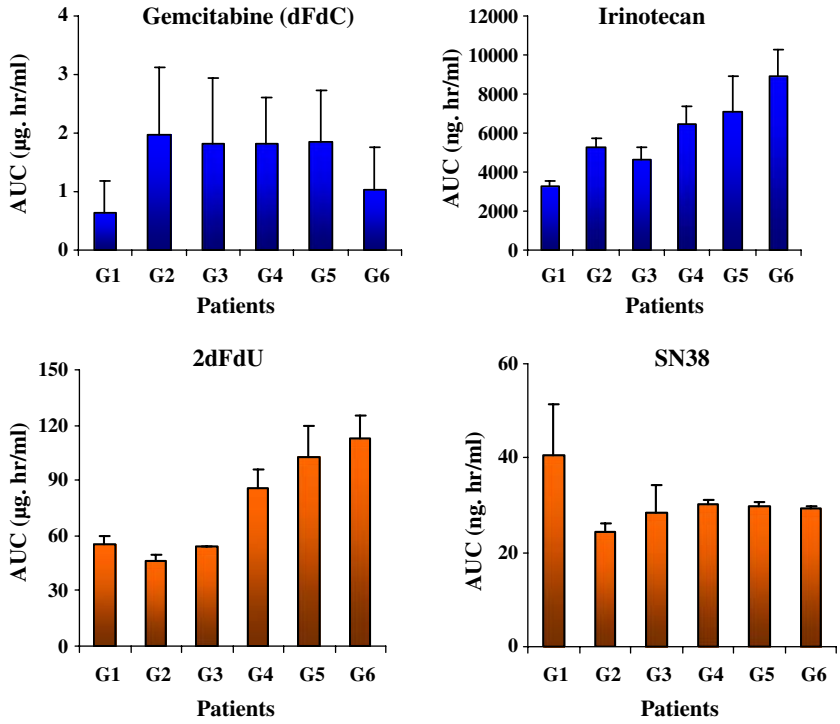

Fig. 3 AUC of CPT-11, SN-38, gemcitabine (dFdc) and its metabolite 2dFdU (G1–G2 stands for dose levels 1–6)

24-h infusion of irinotecan with 5-FU was evaluated [28]. Acute irinotecan-associated cholinergic symptoms are thought to be due to inhibition of human acetylcholinesterase by the lactone form of irinotecan. The cholinergic syndrome is more likely to occur at higher irinotecan dose levels and is associated with the onset of peak irinotecan plasma levels [17, 28, 36–38]. The observation that no patient experienced acute cholinergic symptoms in this trial is likely due to the lower C_{max} levels compared to administration of 125 mg/m^2/90 min.

Conclusion

The combination of gemcitabine and irinotecan administered on days 1, 2 and 15, 16 every 28 days was feasible and well-tolerated in patients with advanced malignancies. Both pretreated patients and chemonaive patients seem to tolerate higher doses of this combination without significant toxicities. This schedule and combination demonstrated activity in a variety of solid tumors, in particular cholangiocarcinoma and small cell lung cancer and merits further evaluation.

References

1. Hertel LW, Boder GB, Kroin JS et al (1990) Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). Cancer Res 50:4417–4422
2. Takimoto CH, Arbuck SA (1996) Camptothecin analogs. In: Chabner BA, Longo DL (eds) Cancer chemotherapy & biotherapy. Principles & practice. Lippincott-Raven Publishers, Philadelphia
3. Bahadori HR, Rocha Lima CM, Green MR, Safa AR (1999) Synergistic effect of gemcitabine and irinotecan (CPT-11) on breast and small cell lung cancer cell lines. Anticancer Res 19(6B):5423–5428
4. Rocha Lima CM, Eckardt JR, Leong SS, Sherman CA, Perkel JA, Putman T, Safa AR, Bahadori HR, Green MR (1999) Single-agent gemcitabine and gemcitabine/irinotecan combination (irimogem) in non-small cell lung cancer. Semin Oncol 26(5 Suppl 16):43–50
5. Rocha Lima CM, Savarese D, Bruckner H, Dudek A et al (2002) Irinotecan plus gemcitabine induce both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. J Clin Oncol 20(5):1182–1191
6. Alberts SR, Erlichman C, Sloan J, Okuno SH, Burch PA, Rubin J, Pitot HC, Goldberg RM, Adjei AA, Atherton PJ, Kaufmann SH (2001) Phase I trial of gemcitabine and CPT-11 given weekly for four weeks every six weeks. Ann Oncol 12(5):627–631
7. Braakhuis BJM, Ruiz van Haperen VWT et al (1995) Schedule-departmet antitumor effect of gemcitabine in in vivo model systems. Semin Oncol 22(Suppl):42–46
8. Ruiz van Halperen VWT, Veerman G, Vermorken JB, Peters GJ (1994) Improved antitumor effect of 2′,2′-difluorodeoxycytidine (gemcitabine) in murine colon carcinomas, when administered as continuous infusions. Proc Am Assoc Cancer Res 35:447
9. Abbruzzese JL, Grunewald R, Weeks EA et al (1991) A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 9:491–498
10. Gandhi V, Plunkett W, Du M, Ayres M, Estey E (2000) Prolonged infusion of gemcitabine: clinical and pharmacodynamic studies during a phase I trial in relapsed acute myelogenous leukemia. J Clin Oncol 20(3):665–673

11. Boven E, Schipper H, Erkelens CAM et al (1993) The influence of the schedule and the dose of gemcitabine on the antitumour efficacy in experimental human cancer. Br J Cancer 68:52–56
12. Grunewald R, Kantajian H, Du M et al (1992) Gemcitabine (2′, 2′ difluorodeoxycytidine) in leukemia: a phase I clinical, plasma and celluler pharmacology study. J Clin Oncol 10:406–413
13. Tempero M, Plunkett W, Ruiz van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21(18):3402–3408
14. von Delius S, Lersch C, Schulte-Frohlinde E, Mayr M, Schmid RM, Eckel F (2005) Phase II trial of weekly 24-hour infusion of gemcitabine in patients with advanced gallbladder and biliary tract carcinoma. BMC Cancer 5(1):61
15. Takimoto CH, Morrison G, Harold N et al (2000) A phase I & pharmacologic study of irinotecan administered as a 96-hour infusion weekly to adult cancer patients. J Clin Oncol 18:659–667
16. Herben VMM, Schellens JHM, Swart M et al (1999) Phase I & pharmacokinetic study of irinotecan administered as a low-dose, continuous infusion over 14 days in patients with solid tumors. J Clin Oncol 17:1897–1905
17. Haaz MC, Rivory LP, Riche C et al (1997) The transformation of irinotecan (CPT-11) to its active metabolite SN-38 by human liver microsomes: differential hydrolysis for the lactone and carboxylate forms. Naunyn Schmiedebergs Arch Pharmacol 356:257–262
18. Slatter JG, Su P, Sams JP et al (1998) Bioactivation of the anticancer agent CPT-11 to SN-38 by human hepatic microsomal carboxylesterases and the in vitro assessement of potential drug interactions. Drug Metab Dispos 25:1157–1164
19. Gupta E, Lestingi TM, Mick R et al (1994) Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res 54:3723-3725
20. Yamazaki H, Funakoshi S, Hirano A et al. (1999) Phase I & pharmacokinetic study of irinotecan (CPT-11) given by 24 hours infusion plus oral uracil/tegafur (UFT) in patients with lung cancer. Proc Am Soc Clin Oncol 18: abstr 2036
21. Salman HS, Tanaka K, Sparano JA (2000) Phase I/II trial of gemcitabine plus cyclophosphamide in patients with metastatic breast carcinoma previously treated with taxanes. Clin Breast Cancer 2(4):299–303
22. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
23. Keith B, Xu Y, Grem JL (2003) Measurement of the anti-cancer agent gemcitabine in human plasma by high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 785(1):65–72
24. Yilmaz B, Kadioglu Y (2004) Comparison of zero- and second-order derivative spectrophotometric and HPLC methods for the determination of gemcitabine in human plasma. Farmaco 59(5):425–429
25. Rivory LP, Chatelut E, Canal P, Mathieu-Boue A, Robert J (1994) Kinetics of the in vivo interconversion of the carboxylate and lactone forms of irinotecan (CPT-11) and of its metabolite SN-38 in patients. Cancer Res 54:6330–6333
26. Rivory LP, Bowles MR, Robert J, Pond SM (1996) Conversion of irinotecan (CPT-11) to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38) by human liver carboxylesterase. Biochem Pharmcol 52:1103–1111
27. Wang H, Wang S, Nan L, Yu D, Agrawal S, Zhang R (2002) Antisense anti-MDM2 mixed-backbone oligonucleotides enhance therapeutic efficacy of topoisomerase I inhibitor irinotecan in nude mice bearing human cancer xenografts: In vivo activity and mechanisms. Int J Oncol 20:745–752
28. Wright MA, Morrison G, Lin P et al. (2005) A phase I pharmacologic and pharmacogenetic trial of sequential 24-hour infusion of irinotecan followed by leucovorin and a 48-hour infusion of fluorouracil in adult patients with solid tumors. Clin Cancer Res 11(11):4144–4150
29. Piantadosi S (1997) Clinical trials: a methodologic perspective. Wiley, New York, pp 151–155
30. Saif MW, Sellers S, Russo S (2006) Gemcitabine-related radiation recall in a patient with pancreatic cancer. Anticancer Drugs 17(1):107–111
31. Ulrich-Pur H, Kornek GV, Fiebiger W, Schull B, Raderer M, Scheithauer W (2001) Treatment of advanced hepatocellular carcinoma with biweekly high-dose gemcitabine. Oncology 60(4):313–315
32. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B, Scheithauer W (2001) Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 12(2):183–186
33. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR (2003) Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 21(5):807–814
34. Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905–914
35. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15(6):2403–2413
36. Stewart DF, Ma M, Furman WL et al (1998) Pharmocokinetics of inrinotecan and its active metabolite SN-38 in children with recurrent solid tumors after protracted low dose IV irinotecan. Proc Am Soc Clin Oncol 17:186a
37. Slatter JG, Schaaf LJ, Sams JP, Feenstra KL, Johnson MG, Bombardt PA, Cathcart KS, Verburg MT, Pearson LK, Compton LD, Miller LL, Baker DS, Pesheck CV, Lord RS (2000) Pharmacokinetics, metabolism and excretion of irinotecan (CPT-11) following I.V. infusion of [^{14}C] CPT-11 in cancer patients. Drug Metab Dispos 28:423–433
38. Mathijssen RHJ, Loos WJ, Verweij J, Sparreboom A (2002) Pharmacology of topoisomerase I inhibitors irinotecan (CPT-11) and topotecan. Curr Cancer Drug Target 2:103–123