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ORIGINAL ARTICLE

A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer

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Abstract
Purpose The aim of this study was to assess the efficacy and toxicity of weekly irinotecan in patients with metastatic pancreatic cancer.
Patients and methods Patients with histologically proven pancreatic adenocarcinoma, at least one bidimensionally measurable metastatic lesion, and no prior chemotherapy were selected. Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. Pharmacokinetics was examined on day 1 of the first cycle of treatment.
Results Thirty-seven of 40 enrolled patients were assessable for efficacy and toxicity. A partial response was obtained in 10 patients, giving an overall response rate of 27.0% (95% confidence interval 13.8–44.1%). The median overall survival was 7.3 months with a 1-year survival rate of 29.5%. Although toxicities were generally tolerated, one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. Pharmacokinetic study showed that patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.
Conclusion Single-agent irinotecan has significant efficacy for metastatic pancreatic cancer. The toxicity with this schedule appears manageable, though it must be monitored carefully.

Keywords Irinotecan · Phase II study · Pancreatic cancer · Chemotherapy · Pharmacokinetics

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Introduction

Pancreatic cancer is a highly aggressive disease, with approximately 21,000 deaths annually in Japan [7]. While surgery remains the only potential curative option for this disease, the vast majority of patients unfortunately present with advanced, unresectable disease. Although it has been demonstrated that gemcitabine is

an effective tool for palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer [2], single-agent gemcitabine has shown limited benefit, with objective response rates of less than 15% and a median overall survival of around 4–6 months [2, 4, 5]. Therefore, there is a clear need to identify a new effective chemotherapeutic regimen for pancreatic cancer.

Irinotecan is a water-soluble semisynthetic derivative of camptothecin, a plant alkaloid obtained from the *Camptotheca acuminata* tree. Irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), bind to topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing double-stranded DNA breaks and consequent tumor cell death. Irinotecan is internationally approved for use in metastatic colorectal cancer, and has broad activity against other malignancies including lung cancer [6, 9, 15, 16]. Although several studies of single-agent irinotecan or irinotecan-based chemotherapy against pancreatic cancer have been reported [11, 12, 14, 18, 22], the role of irinotecan in the treatment of patients with pancreatic cancer remains unclear yet. Because there are few effective agents for pancreatic cancer to date, it is important to determine the clinical efficacy of irinotecan for this disease. We, therefore, conducted an open-label, multicenter, single-arm phase II study to evaluate the efficacy and toxicity of single-agent irinotecan in patients with pancreatic cancer. In the current study, we adopted weekly administration of irinotecan because safety of this schedule has been confirmed in other cancers in Japan [6, 9, 16]. Since patients with pancreatic cancer tend to suffer various tumor-related complications such as obstructive jaundice and impaired liver function, pharmacokinetic study was also performed.

Patients and methods

Patient selection

Patients were entered into the study if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; at least one bidimensionally measurable metastatic lesion; no history of prior chemotherapy or radiotherapy; age 20–74 years; Karnofsky performance status (KPS) ≥ 50 points; estimated life expectancy ≥ 2 months; adequate bone marrow function (WBC count $< 12{,}000$ per mm^3, neutrophil count $\geq 2{,}000$ per mm^3, platelet count $\geq 100{,}000$ per mm^3, and hemoglobin level ≥ 10.0 g/dl), adequate renal function (serum creatinine and blood urea nitrogen level $\leq$ the institutional upper limit of normal), and adequate liver function (serum total bilirubin level ≤ 2.0 mg/dl, serum transaminases levels ≤ 2.5 times the institutional upper limit of normal); and written informed consent. Patients were excluded if there was a history of severe drug hypersensitivity; serious complications; central nervous system metastases; other concomitant malignant disease; marked pleural or peritoneal effusion; and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board of each participating center, and conducted in accordance with Good clinical practice guideline in Japan.

Treatment plan

This study was an open-label, multicenter, single-arm phase II study. Irinotecan was supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsha Co., Ltd. (Tokyo, Japan). Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue. Prophylactic administration of antiemetic agents was allowed at the investigator's discretion. Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during treatments. If patients experienced neutropenia of $< 1{,}500$ per mm^3, thrombocytopenia of $< 100{,}000$ per mm^3, fever ($\geq 38°C$) with suspected infection, grade ≥ 1 or watery diarrhea, or $\geq$ grade 3 non-hematological toxicities other than nausea, vomiting and anorexia, irinotecan administration was omitted on that day and postponed to the next scheduled treatment day. If patients experienced neutropenia of < 500 per mm^3, thrombocytopenia of $< 50{,}000$ per mm^3, fever ($\geq 38°C$) with suspected infection, or grade ≥ 2 or watery diarrhea at any time, the irinotecan dose of the subsequent cycle was reduced by 20 mg/m^2. Patients went off study if they required more than two dose reductions. If the next cycle could not start within 4 weeks from the scheduled day, the patient was withdrawn from the study. The toxicity of irinotecan therapy was evaluated according to the National Cancer Institute Common Toxicity criteria version 2.0.

Evaluation

Objective tumor response was evaluated every 4 weeks according to the Japan Society for Cancer Therapy (JSCT) criteria [8], which is similar to the WHO crite-

ria. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. A partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. No change (NC) was defined as a $< 50\%$ reduction or a $< 25\%$ increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. Progressive disease (PD) was defined as a $\geq 25\%$ increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [1]. Objective tumor response was secondarily assessed according to the response evaluation criteria in solid tumors (RECIST criteria) [20] among patients with at least one measurable metastatic lesion whose longest diameter measured by CT is no less than double the slice thickness. An external review committee confirmed objective responses and toxicities.

Clinical benefit was evaluated on the basis of established criteria [13]. Each patient was classified as a clinical benefit responder or non-responder on the basis of the change in two parameters of clinical benefit (pain and KPS). In the current study, the body weight was not used to evaluate clinical benefit response because the body weight of patients with pancreatic cancer sometimes increases due to not only improvement of their condition but also retention of malignant ascites. A positive response for pain was defined as an improved pain intensity of $\geq 50\%$ from baseline for ≥ 4 weeks, or a decreased morphine consumption of $\geq 50\%$ from baseline for ≥ 4 weeks. A positive response for KPS was defined as an improved KPS of ≥ 20 points from baseline for ≥ 4 weeks. To be classified as a clinical benefit responder, a patient had to achieve a positive response in at least one parameter (pain or KPS) without being negative for the other, sustained for ≥ 4 weeks.

Pharmacokinetics

To investigate the impact of biliary drainage on pharmacokinetics of irinotecan, we planned to recruit five patients each with and without biliary drainage. Heparinized blood samples (5 ml) for the pharmacokinetic study were obtained before infusion of irinotecan, at the end of the 90 min infusion, and 0.5, 1, 2, 4, 6, 8, 24 h after the completion of infusion on day 1 of the first cycle. Blood samples were immediately centrifuged at 3,000 rpm for 10 min to remove plasma and stored in polyethylene tubes at $-20^{\circ}C$ until analysis. Quantitative analysis of total irinotecan and its metabolites, SN-38, SN-38 glucuronide, and 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) was performed by methods previously described [17, 19].

Statistical analysis

The primary goal was to evaluate the response rate (CR and PR) of irinotecan. The 95% confidence interval for response rate was calculated based on the binomial distribution. The response duration was defined as the interval from the first documentation of response to the first documentation of tumor progression. The time to progression (TTP) was calculated from the date of study enrollment to the first documentation of tumor progression; and overall survival was calculated from the date of study enrollment to the date of death or the last follow-up with censored value. Median overall survival and the median TTP were estimated by the Kaplan–Meier method and 95% confidence interval were estimated based on the Greenwood's formula. A total of 35 patients were planned to be enrolled based on the assumptions that the expected response rate of irinotecan was 15% and the threshold rate was 5%. A two-stage design was used in this study. The interim analysis was planned when 15 patients were enrolled in the first stage of the study. If the upper limit of the 90% confidence interval (one-sided) did not exceed the expected rate of 15% (no objective response in the 15 patients), irinotecan was judged to be ineffective and the study was ended. If an objective response was observed in any of the first 15 patients, additional 20 patients were enrolled in the second stage of accrual to estimate the response rate. If 6 or more out of 35 patients achieved objective response, the lower limit of the 95% confidence interval (two-sided) exceeds the threshold rate of 5%, and then the agent would be considered to be active for metastatic pancreatic cancer.

Results

Patients

Forty patients were enrolled in the study by 7 institutions between August 2001 and November 2002. Of the 40 patients, 3 patients who did not receive irinotecan because of rapid tumor progression or protocol violation were excluded from analysis. Patient characteristics of the remaining 37 patients are listed in Table 1.

All 37 patients had metastatic disease and had a good KPS of ≥ 80. Morphine was prescribed for 10 patients due to abdominal or back pain and 14 patients were assessable for clinical benefit response. Seven patients had recurrent disease after pancreatic resection. Two patients underwent percutaneous transhepatic biliary drainage for obstructive jaundice prior to study enrollment.

Treatments

Data were collected through May 4, 2004, providing 18 months of survival follow-up from the time accrual ended. Thirty-seven patients were given a total of 108 cycles of therapy, with a median of 2 cycles each (range 1–10). The administration of irinotecan on day 8 and day 15 was performed in 87 (80.6%) and 76 (70.4%) of 108 cycles, respectively. Dose reduction was required in 13 patients (35.1%), mainly due to diarrhea and fever with suspected infection. At the time of analysis, all patients had discontinued the study because of disease progression ($n = 28$), toxicity ($n = 5$), treatment-related death ($n = 1$), and withdrawal of consent due to other reasons ($n = 3$). After discontinuation of irinotecan, 26 patients received gemcitabine monotherapy or gemcitabine-based combination therapy; one patient was treated with S-1, and remaining 10 patients underwent only supportive care. Among 27 patients treated with second-line chemotherapy, 2 patients who received gemcitabine monotherapy achieved a PR.

Table 1 Patient characteristics ($n = 37$)

Characteristics		No. of patients (%)
Gender		
Male		25 (67.6)
Female		12 (32.4)
Median age, years (range)	59 (41–74)	
Karnofsky performance status, point		
100		8 (21.6)
90		25 (67.6)
80		4 (10.8)
Median body surface area (m^2) (range)	1.55 (1.31–1.85)	
History of surgical resection		7 (18.9)
PTBD		2 (5.4)
Sites of metastasis		
Liver		33 (89.2)
Lymph nodes		17 (45.9)
Lung		8 (21.6)
Others		3 (8.1)

PTBD percutaneous transhepatic biliary drainage

Efficacy

Of 37 patients, 10 patients achieved a PR according to the JSCT criteria (Table 2). The overall response rate was therefore 27.0% (95% confidence interval 13.8–44.1%) with median response duration of 4.1 months (range 0.9–7.1 months). The median TTP was 2.1 months (range 0.7–9.5 months), and the median overall survival of 7.3 months (range 0.7–25.9 months) with a 1-year survival rate of 29.5% (Fig. 1). Of 29 patients assessable for RECIST criteria, a PR was seen in 8 patients (27.6%), stable disease in 6 patients (20.7%), and PD in 12 patients (41.4%). With regard to clinical benefit, 2 of 14 evaluable patients had pain relief and were classified as a responder (Table 3).

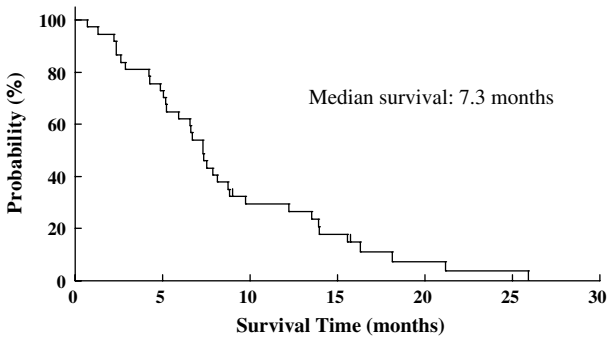

Fig. 1 Overall survival curve of all 37 patients

Table 2 Efficacy results

	No. ($N = 37$)	%
Tumor response		
Partial response	10	27.0
No change	7	18.9
Progressive disease	17	45.9
Not evaluable	3	8.1
Time to progression (months)		
Median	2.1	
Range	0.7–9.5	
Overall survival (months)		
Median	7.3	
Range	0.7–25.9	
1-year survival rate		29.5

Table 3 Clinical benefit response ($n = 14$)

		Karnofsky performance status		
		Improved	Stable	Worse
Pain	Improved	0	2	0
	Stable	0	6	1
	Worse	0	5	0

Toxicity

All 37 patients were assessable for toxicity. The major toxicities observed during the study are summarized in Table 4. The most common toxicities were hematological toxicity and gastrointestinal toxicity. Grade 3 or 4 neutropenia occurred in 10 patients (27.0%) and 5 patients received granulocyte-colony stimulating factors. The neutrophil count nadir typically occurred on day 21, and recovered to baseline values by day 28. Although nausea, vomiting, and anorexia were observed frequently, most of these toxicities recovered spontaneously or with adequate supportive treatment. Grade 3 diarrhea occurred in four patients and they were treated with loperamide. Most diarrheas appeared during the first cycle of treatment: the median time to the worst day of diarrhea was 13 days from the initiation of a cycle of therapy. Though the toxicities were mild to moderate in severity and short in duration, one patient died at day 21 of the first cycle of treatment because of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and watery diarrhea due to irinotecan. The patient, a 58-year old woman with pretreatment KPS of 100, developed grade 4 neutropenia on day 12 complicated by fever (38.8°C) and grade 3 diarrhea that evolved to fatal shock despite aggressive medical management.

Table 4 Treatment-related adverse events ($n = 37$): worst grade reported during treatment period

Toxicity	Grade				Grade 1–4 (%)	Grade 3–4 (%)
	1	2	3	4		
Hematologic						
Leukopenia	15	6	8	1	81.1	24.3
Neutropenia	5	11	8	2	70.3	27.0
Anemia	0	14	3	0	45.9	8.1
Thrombocytopenia	1	1	1	1	10.8	5.4
Non-hematologic						
Nausea	7	12	15	–	91.9	40.5
Vomiting	7	14	5	0	70.3	13.5
Diarrhea	15	8	4	0	73.0	10.8
Constipation	1	8	2	0	29.7	5.4
Anorexia	4	7	14	1	70.3	40.5
Stomatitis	2	0	0	0	5.4	0
Rash	1	0	0	0	2.7	0
Alopecia	24	1	–	–	67.6	–
Fatigue	3	8	1	1	35.1	5.4
Fever	3	1	0	0	10.8	0
Infection	2	1	4	1	21.6	13.5
Total bilirubin	4	1	1	0	16.2	2.7
AST	5	5	2	0	32.4	5.4
ALT	4	4	3	0	29.7	8.1
Hyponatremia	6	0	3	0	24.3	8.1
Creatinine	0	0	2	0	5.4	5.4

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Pharmacokinetics

A pharmacokinetic analysis was performed in five patients without biliary drainage and in two patients who underwent percutaneous transhepatic biliary drainage (Planned five patients could not be enrolled in drainage group because only two patients had biliary drainage in the current study). Table 5 and Fig. 2 show the pharmacokinetic parameters for irinotecan and its three major metabolites in patients with and without biliary drainage. Although it was difficult to assess the influence of biliary drainage in this study because of the small number of subjects analyzed, patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.

Discussion

The prognosis of the patients with pancreatic cancer remains poor even after a randomized study demonstrated survival advantage of gemcitabine against advanced pancreatic cancer, indicating necessity of new effective agents or combination regimens for this dismal disease. Irinotecan, which has a quite different mechanism from gemcitabine, has been considered one of the attractive agents for pancreatic cancer, since this agent has demonstrated substantial activity in various types of malignant tumor [6, 9, 15, 16]. The current multicenter phase II study was, therefore, conducted to evaluate the efficacy and toxicity of single-agent irinotecan in patients with metastatic pancreatic cancer.

In this study, we found that weekly irinotecan demonstrated a good overall response rate of 27.0% in 37 patients with metastatic pancreatic cancer. In addition, a relatively long median overall survival of 7.3 months was shown, though all patients in our study had metastatic disease. As to clinical benefit response, 2 of 14 patients achieved clinical benefit response. These results indicate that irinotecan has a substantial antitumor effect on pancreatic cancer.

The major toxicities of irinotecan that were seen in the study were myelosuppression and gastrointestinal toxicities, similar to the previous observation of irinotecan monotherapy in other cancers [6, 9, 16]. Most toxicity was mild to moderate, and manageable with conservative treatment. However, one patient died of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and diarrhea. Pretreatment condition of this patient was good (KPS = 100), and it was difficult to predict these

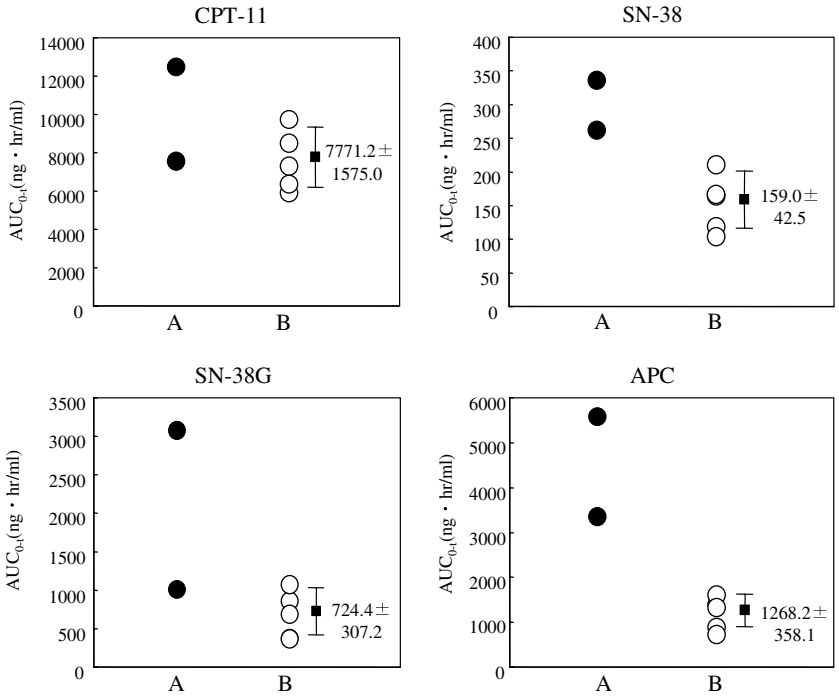

Fig. 2 Area under the concentration versus time curve for irinotecan and metabolites in patients with biliary drainage (*A*, $n = 2$) and without drainage (*B*, $n = 5$). The values are expressed as the mean ± SD

Table 5 Pharmacokinetic parameters after single administration of irinotecan at a dose of 100 mg/m^2 ($n = 7$)

		C_{max} (ng/ml)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-t} (ngh/ml)	CL (l/h m^2)
Irinotecan	A	1,188.5, 1,997.6	1.6, 1.5	7.8, 8.2	7,762, 12,692	11.8, 7.1
	B	1,701.0 ± 348.3	1.5 ± 0.1	7.7 ± 0.9	7,771.2 ± 1,575.0	12.4 ± 2.5
SN-38	A	25.5, 26.2	2.1, 1.5	14.7, 9.9	268, 342	–
	B	17.5 ± 3.8	2.3 ± 0.8	30.2 ± 27.6	159.0 ± 42.5	
SN-38G	A	81.3, 207.2	3.6, 2.0	10.8, 12.5	1,063, 3,130	–
	B	78.8 ± 34.1	2.2 ± 0.2	21.6 ± 13.2	724.4 ± 307.2	
APC	A	309.2, 359.3	2.6, 5.5	7.0, 9.5	3,441, 5,673	–
	B	116.6 ± 39.7	3.0 ± 0.6	8.8 ± 0.7	1,268.2 ± 358.1	

A Patients with biliary drainage $n = 2$

B Patients without biliary drainage (parameters are represented as the mean ± SD) $n = 5$

episodes before onset. Although our study indicated that weekly irinotecan administration would be tolerable in patients with metastatic pancreatic cancer, careful observation is required during the treatment period, since pancreatic cancer patients tend to suffer various tumor-related complications and easily take a turn to the worse because of tumor progression.

There are two studies of single-agent irinotecan that assessed efficacy and toxicity against pancreatic cancer [14, 22]. Sakata et al. [14] studied irinotecan at a dose of 100 or 150 mg/m^2 administered weekly or bi-weekly to previously treated or untreated patients with pancreatic cancer in Japan. Although 57 of 61 enrolled patients were assessable, only 4 patients (7.0%) showed a PR. This study included 28 patients (49.1%) with poor performance status of 2–3 and 22 patients (38.6%) with prior chemotherapy, and no patient showed a PR in these patients with poor performance status or prior chemotherapy. Wagener et al. [22] demonstrated that irinotecan at a dose of 350 mg/m^2 administered every 3 weeks to chemo-naïve pancreatic cancer patients with performance status of ≤ 2, achieved a PR in 3 of 32 assessable patients (9.4%) with an median overall survival of 5.2 months. Although precise reason for the discrepant response rates between our study and the other two studies is unclear, patient background may be one possible explanation because only chemo-naïve patients with good performance status were entered into our study (89.2% of our patients had good KPS of ≥ 90).

For the purpose of the improvement on response rate and prognosis, several studies of combination therapy have been conducted in patients with pancreatic cancer. With regard to irinotecan with gemcitabine, an

encouraging activity, response rates between 20.0 and 24.7% and median overall survival between 5.7 and 7 months, have been reported in two phase II studies [11, 18]. However, survival benefit of this combination therapy was not shown in a phase III study [12], in which, 360 patients were randomized to treatment with a combination of gemcitabine 1,000 mg/m^2 followed by irinotecan 100 mg/m^2 given on days 1 and 8 of a 3-week cycle versus gemcitabine monotherapy. The response rate for the combination therapy was higher at 16.1% compared with 4.4% for gemcitabine alone, but there was no difference in median overall survival (6.3 vs. 6.6 months). However, several clinical studies have recently indicated that irinotecan-based chemotherapy seemed to be an effective treatment for advanced pancreatic cancer after gemcitabine failure: irinotecan–raltitrexed combination demonstrated overall response rate of 16% (3/19) in patients with gemcitabine-pretreated pancreatic cancer [21], and Cantore et al. [3] reported that irinotecan plus oxaliplatin showed response rate of 10% (3/30) with a clinical benefit response of 20% (6/30) for patients with advanced pancreatic cancer after gemcitabine failure.

Because biliary excretion is a major elimination pathway for irinotecan and its metabolites, we investigated the impact of biliary drainage on the pharmacokinetics for this agent. Our results suggested that patients with biliary drainage tended to have higher area under the concentration versus time curve of irinotecan and metabolites compared with patients without biliary drainage. Meyerhardt et al. [10] reported that modest elevation of bilirubin (1.0–1.5 mg/dl) is associated with increased grade 3 to 4 neutropenia in patients treated with irinotecan. The fact that the two patients with biliary drainage in the current study had slight elevation of baseline serum bilirubin level (1.4 and 1.7 mg/dl) might influence pharmacokinetics for irinotecan. Although no severe hematological or non-hematologic toxicities appeared in these two patients, careful observation may be required when treating patients with biliary drainage.

In conclusion, single-agent irinotecan showed a substantial antitumor activity for patients with metastatic pancreatic cancer, rendering a 27.0% response rate. The toxicity with this schedule appears manageable, though it must be monitored carefully.

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References

1. Aoki K, Okada S, Moriyama N, Ishii H, Nose H, Yoshimori M, Kosuge T, Ozaki H, Wakao F, Takayasu K, Mukai K (1994) Accuracy of computed tomography in determining pancreatic cancer tumor size. Jpn J Clin Oncol 24:85–87
2. Burris HA 3rd, 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 15:2403–2413
3. Cantore M, Rabbi C, Fiorentini G, Oliani C, Zamagni D, Iacono C, Mambrini A, Del Freo A, Manni A (2004) Combined irinotecan and oxaliplatin in patients with advanced pretreated pancreatic cancer. Oncology 67:93–97
4. Carmichael J, Fink U, Russell RG, Spittle MF, Harris AL, Spiessi G, Blatter J (1996) Phase II study of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer 73:101–105
5. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG (1994) Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 12:29–34
6. Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S, Masuda N, Nakajima S, Taguchi T (1992) A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. CPT-11 Lung Cancer Study Group. J Clin Oncol 10:16–20
7. http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei03/hyo5.html (accessed August 18, 2005)
8. Japan Society for Cancer Therapy: Criteria for the evaluation of the clinical effects of solid cancer chemotherapy (1993) J Jpn Soc Cancer Ther 28:101–130
9. Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Negoro S, Nishioka M, Nakagawa K, Takada M (1992) CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 10:1225–1229
10. Meyerhardt JA, Kwok A, Ratain MJ, McGovren JP, Fuchs CS (2004) Relationship of baseline serum bilirubin to efficacy and toxicity of single-agent irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 22:1439–1446
11. Rocha Lima CM, Savarese D, Bruckner H, Dudek A, Eckardt J, Hainsworth J, Yunus F, Lester E, Miller W, Saville W, Elfring GL, Locker PK, Compton LD, Miller LL, Green MR (2002) Irinotecan plus gemcitabine induces both radiographic and CA 19–9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. J Clin Oncol 20:1182–1191
12. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL (2004) Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 22:3776–3783
13. Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA 3rd, Green MR, Tarassoff PG, Brown TD, Casper ES, Storniolo AM, Von Hoff DD (1996) A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol 7:347–353

14. Sakata Y, Shimada Y, Yoshino M, Kambe M, Futatsuki K, Nakao I, Ogawa N, Wakui A, Taguchi T (1994) A late phase II study of CPT-11, irinotecan hydrochloride, in patients with advanced pancreatic cancer (in Japanese). CPT-11 study group on gastrointestinal cancer. Jpn J Cancer Chemother 21:1039–1046
15. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905–914
16. Shimada Y, Yoshino M, Wakui A, Nakao I, Futatsuki K, Sakata Y, Kambe M, Taguchi T, Ogawa N (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. J Clin Oncol 11:909–913
17. Sparreboom A, de Bruijn P, de Jonge MJA, Loos WJ, Stoter G, Verweij J, Nooter K (1998) Liquid chromatographic determination of irinotecan and three major metabolites in human plasma, urine and feces. J Chromatogr B Biomed Sci Appl 712:225–235
18. Stathopoulos GP, Rigatos SK, Dimopoulos MA, Giannakakis T, Foutzilas G, Kouroussis C, Janninis D, Aravantinos G, Androulakis N, Agelaki S, Stathopoulos JG, Georgoulias V (2003) Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study by the Greek Cooperative Group for Pancreatic Cancer. Ann Oncol 14:388–394
19. Tanaka S, Yoshida Y, Suzuki W, Sudo K, Hakusui H (1994) A new HPLC method for the determination of irinotecan hydrochloride (CPT-11) and its metabolite, SN-38 in human plasma and urine (in Japanese). Jpn Pharmacol Ther 22:163–172
20. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
21. Ulrich-Pur H, Raderer M, Verena Kornek G, Schull B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W (2003) Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. Br J Cancer 88:1180–1184
22. Wagener DJ, Verdonk HE, Dirix LY, Catimel G, Siegenthaler P, Buitenhuis M, Mathieu-Boue A, Verweij J (1995) Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. Ann Oncol 6:129–132