

Pilot study of irinotecan/oxaliplatin (IROX) combination chemotherapy for patients with gemcitabine- and 5-fluorouracil- refractory pancreatic cancer

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Summary Background Gemcitabine- and 5-fluorouracil (5-FU)- based chemotherapy is a commonly used adjuvant or palliative treatment for patients with pancreatic cancer. However, a standard chemotherapy regimen has yet to be developed for patients refractory to gemcitabine and 5-FU treatment. We attempted to evaluate the efficacy and safety of a combination of irinotecan and oxaliplatin (IROX) as a

salvage treatment for patients with gemcitabine- and 5-FU-refractory pancreatic cancer. *Patients and Methods* Patients with advanced pancreatic cancer who were refractory to prior gemcitabine- and 5-FU- based chemotherapy were enrolled in this study. IROX chemotherapy was administered as follows: Irinotecan, 150 mg/m² on day 1; and oxaliplatin, 85 mg/m² on day 1 over 90 min every 2 weeks. *Result* From Mar. 2006 to Dec. 2008, a total of 14 patients were administered 50 cycles of chemotherapy. The male-to-female ratio of the patient group was 11:3. These patients ranged in age from 48 to 73 years (median 65.5 years old). 3 patients (21.4%) evidenced partial response. four patients (28.6%) exhibited stable disease. The median time to progression and overall survival time were 1.4 (95% CI: 1.2–1.6) months and 4.1 (95% CI: 2.0–6.2) months, respectively. Major hematologic toxicities included grade 1–2 anemia (88%), neutropenia (36%), thrombocytopenia (30%), and grade 3–4 neutropenia (10%). The most frequently detected non-hematological toxicities were grade 3 diarrhea (14%). *Conclusion* The IROX regimen appears to constitute a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who have been previously treated with gemcitabine- and 5-FU-based chemotherapy.

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Introduction

The role of chemotherapy in pancreatic cancer patients has been the subject of a great deal of controversy. Gemcitabine

has been extensively utilized as a standard first-line chemotherapy agent in cases of advanced pancreatic cancer [1]. Recent large randomized phase III trials in cases of advanced pancreatic cancer have shown that the addition of capecitabine or erlotinib to gemcitabine yield results superior to those noted with single-agent gemcitabine treatment [2, 3]. Despite several efforts, the efficacy of gemcitabine on the course of the disease has proven marginal, as was also the case with the progress of advanced pancreatic cancer within 4 months after gemcitabine-based first-line chemotherapy [4, 5]. Additionally, patients with advanced pancreatic cancer have been shown to have a 5-year survival rate of less than 5% [5, 6].

Prior to the appearance of gemcitabine, 5-fluorouracil was the drug most frequently utilized for the treatment of advanced pancreatic cancer. 5-fluorouracil-based multi-drug combination regimens have been reported previously to confer a survival advantage over best supportive care in cases of advanced pancreatic cancer [7]. Furthermore, the treatment of advanced pancreatic cancer patients after failure with first-line chemotherapy remains controversial. Owing to poor performance status and rapid clinical deterioration, approximately half of advanced pancreatic cancer patients who evidence progression after gemcitabine-based chemotherapy are ineligible for second-line chemotherapy. Therefore, only a limited number of studies have addressed the role of second-line chemotherapy in cases of advanced pancreatic cancer.

Irinotecan (CPT-11) is a semisynthetic, watersoluble derivative of the plant alkaloid camptothecin. After conversion to its active metabolite, SN-38, irinotecan functions by inhibiting DNA topoisomerase I, thereby interfering with DNA replication and cell division [8]. The results of an irinotecan-containing regimen in the treatment of gastrointestinal cancers have been relatively encouraging [9, 10]. Irinotecan is also highly active on pancreatic tumor cells in culture, and also in xenograft models [11]. Irinotecan monotherapy has been previously tested in patients with previously untreated advanced pancreatic cancer [12].

Oxaliplatin, a third-generation platinum analogue, is a diamminocyclohexane platinum which forms interstrand DNA adducts, which differ from those formed by cisplatin or carboplatin in terms of their capability to overcome resistance mechanisms. Preclinical studies have suggested that pancreatic cancer cell lines are highly sensitive towards raltitrexed and oxaliplatin even in gemcitabine- and 5-fluorouracil-resistant cells [13, 14], and oxaliplatin evidences an additive antitumor activity when combined with raltitrexed or other thymidylate synthase inhibitors [15].

Herein, we have attempted to confirm the efficacy and safety of a combination of irinotecan and oxaliplatin (IROX) as a salvage treatment for patients with gemcitabine- and 5-FU- refractory pancreatic cancer.

Patients and methods

Eligibility

The patients had to have a histologically confirmed diagnosis of adenocarcinoma of the pancreas, as well as at least one measurable lesion. Our study population included patients who had received a previous palliative gemcitabine- based and/or 5-FU based chemotherapy regimen. Cases evidencing progression within 6 months after adjuvant chemotherapy as gemcitabine and/or 5-FU were eligible for inclusion in the study. The Eastern Cooperative Oncology Group (ECOG) performance status was 0–2 in all patients in this study. The patients were also required to harbor no central nervous system metastases, no active infections, no serious or uncontrolled concurrent medical illnesses, and no previous history of any other malignancies. Adequate bone marrow function (absolute neutrophil count (ANC) $\geq 1500 \times 10^3 / \mu\text{L}$, platelet count $\geq 75,000 \times 10^3 / \mu\text{L}$), renal function (serum creatinine $\leq 1.5 \text{ mg/dL}$), and hepatic function (aspartate aminotransferase, alanine aminotransferase $\leq 3 \times$ upper limits of normal, total bilirubin $\leq 1.5 \times$ upper limits of normal) were essential. The study was approved by the local ethics committee, and informed consent was obtained from all patients prior to their entry in this study.

Treatment protocol and evaluation

Patients received oxaliplatin 85 mg/m^2 diluted in 500 ml of 5% dextrose as a 2-hr intravenous infusion on day 1, followed by 150 mg/m^2 of irinotecan diluted in 500 ml 5% dextrose as a 90-min infusion once every 2 weeks. Treatment was continued until signs of disease progression or unacceptable toxic effects developed, or until a patient refused further treatment.

Dose modification for toxicity

Administration of irinotecan or oxaliplatin was delayed if there were non-hematologic toxicities of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or greater, neutropenia of less than $1,500 / \mu\text{L}$, or thrombocytopenia of less than $100,000 / \mu\text{L}$. If the neutrophil count was greater than $1,500 / \mu\text{L}$ and the

Table 1 Patients characteristics

No.	Sex	Age	ECOG PS	Previous OP	Adjuvant treatment ^a	Definitive CCRT ^a	Previous chemotherapy	Metastasis	Cycles	Response	TTP (months)	OS (months)
1	M	48	2	No		RT+X	Gem/Cis	Liver, distant LN	2	PD	0.7	2.2
2	M	73	1	No			Gem/S-1	Liver, lung, bone	2	PD	1.4	3.0
3	M	69	1	No			Gem/S-1	Liver	6	PR	7.4	14.4
4	F	57	2	No			Gem/Cis -> X	Peritoneal seeding	3	SD	7.5	7.7
5	M	67	1	Yes	RT+X		Gem	Liver	2	SD	5.2	5.2
6	M	73	1	No			Gem/S-1 -> Gem/Cis	Liver, distant LN	12	PR	6.2	6.9 ^b
7	F	58	1	Yes	FL		Gem	Liver, peritoneal seeding	3	SD	4.2	5.1
8	M	62	2	No			Gem/5-FU	Liver	1	PD	0.6	1.5
9	M	53	2	No			Gem/Cis -> FAM	Liver, lung, omentum, diaphragm	1	PD	0.9	1.1
10	M	64	1	No			GemX	Liver, distant LN, bone	2	SD	1.3	2.6 ^b
11	M	70	1	Yes	RT+X		Gem	Distant LN	2	PD	0.8	3.1
12	M	67	1	Yes ^c			Gem/5-FU	Liver	2	PD	0.9	4.1
13	M	67	1	No			Gem/S-1->Gem/Cis	Liver	3	PD	1.4	3.9
14	F	48	1	No			Gem/S-1	SMA, SMV	9	PR	4.6	10.5

^a Progression within 6 months after treatment, ^b Alive status, ^c Palliative operation

ECOG PS Eastern Cooperative Oncology Group Performance status, M male, F female, OP operation, CCRT concurrent chemo-radiotherapy, RT radiotherapy, TTP time to progression, OS overall survival, PR partial response, SD stable disease, PD progressive disease, X capecitabine, FL 5-fluorouracil (5-FU)+leucovorin, Gem gemcitabine, S-1; TS-1, Cis cisplatin, FAM 5-FU+adriamycin+mitomycin-C, LN lymph node, SMA superior mesenteric artery, SMV superior mesenteric vein

platelet count was greater than 100,000 / μ L after a one-week delay, chemotherapy was administered without dose reduction. If the ANC was less than 1,500 / μ L or the platelet count was less than 100,000 / μ L after a one-week delay, chemotherapy was delayed for an additional week. In cases in which patients required a delay of longer than 2 weeks for recovery, the patients were taken out of the study. The dose of irinotecan or oxaliplatin was reduced by 25% of the previous dose in cases of toxicities of NCI-CTC grade 3 or greater, diarrhea or mucositis, febrile neutropenia, or hemorrhagic complications due to thrombocytopenia.

Assessment of response

Physical examination, complete blood counts, chemistry, and chest x-rays were conducted after each cycle. Computed tomography (CT) scans were repeated every two cycles, or earlier in cases of clinical deterioration. The responses were evaluated in accordance with RECIST criteria [16]. Complete response (CR) was defined as the disappearance of all evidence of disease and the normalization of tumor markers persisting for at least 2 weeks. Partial response (PR) was defined as a $\geq 30\%$ reduction in uni-dimensional tumor measurements, without the appearance of any new lesions or progression in any existing lesion. Progressive disease (PD) was defined as any of the following: (I) a 20% increase in the sum of the products of all measurable lesions, (II) the appearance of any new lesion, or (III) the reappearance of any lesion that had previously disappeared. Stable disease (SD) was defined as a tumor response that did not fulfill the criteria for CR, PR, or PD.

Dose intensity ($\text{mg}/\text{m}^2/\text{week}$) was calculated as the total cumulative dose divided by the duration of treatment. Relative dose-intensity (RDI) was calculated by dividing the dose-intensity by the planned dose-intensity, and was expressed as a percentage. Planned dose-intensities, which were expressed in terms of $\text{mg}/\text{m}^2/\text{week}$, were 75 for irinotecan and 42.5 for oxaliplatin.

Statistical methods

Time to progression (TTP) and overall survival (OS) rates were calculated via the Kaplan-Meier method. The response duration was defined as the period of time from the initial date of response to treatment to the time of disease progression or recurrence. The time to progression and overall survival were calculated from the initiation of treatment to the first observation of disease progression or death, respectively. All data were analyzed with SPSS software (version 15.0, Chicago-IL)

Results

Patient characteristics

Between May 2006 and December 2008, a total of 14 patients were assigned for treatment at the Gyeongnam Regional Cancer Center, in Jinju, South Korea. The basal characteristics of the patients are listed in Table 1. The male-to-female ratio was 11:3. The median patient age was 65.5 years (range: 48–73 years), and 71.4% (10/14) of the patients exhibited an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The most frequent metastatic site or site of involvement was the liver (78.6%), followed by the distant lymph node (28.6%), and the peritoneum (21.4%), in order of decreasing frequency. All 14 of the patients had been treated with gemcitabine and 5-FU (intravenous or oral) as a palliative chemotherapy. Response to first-line chemotherapy was PR in seven patients (50%) and SD in two patients (14.3%).

Response and survival

The median follow-up duration was 12.7 months (range: 7.0–32.2 months). Among the 14 patients evaluated for their tumor responses, three achieved a partial response, with an overall response rate of 21.4% (95% confidence interval [CI]: 0.0–46.0%). Four patients (28.6%) evidenced stable disease and seven patients (50%) evidenced progression during the course of treatment (Table 2). The median time to progression was 1.4 months (95% CI: 1.2–1.6 months), and the median overall survival time was 4.1 months (95% CI: 2.0–6.2 months) (Fig. 1).

Dose administration and toxicity

14 patients received a total of 50 treatment cycles. Dose reduction was conducted over 23 cycles (46%). The dose intensity ($\text{mg}/\text{m}^2/\text{wk}$) was 62.9 (83.9%) for irinotecan and 36.2 (85.1%) for oxaliplatin. The median number of cycles of IROX treatment was 2 (range, 1–12 cycles). The toxicities observed during the treatment are provided in

Table 2 Response of treatment

Response	N=14	%
CR	0	0
PR	3	21.4
SD	4	28.6
PD	7	50

CR complete response, PR partial response, SD stable disease, PD progression of disease

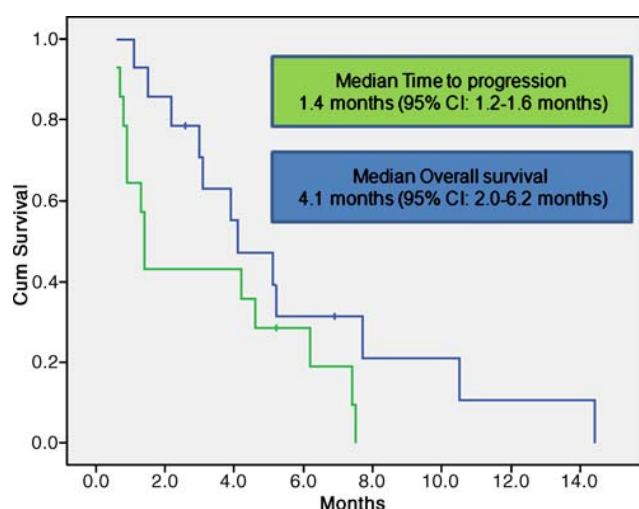


Fig. 1 Time to progression and overall survival curves

Table 3. Grade 1 or 2 anemia and neutropenia were observed in 44 cycles (88%) and 18 cycles (36%), respectively. Grade 3 or 4 neutropenia was observed in 5 cycles (10%), and febrile neutropenia occurred in two cycles (4%). Grade 3 nausea and diarrhea were observed in 1 and 2 patients, respectively. Grade 1 AST/ALT increase was observed in one patient, and grade 1 neuropathy was also observed in 1 patient.

Discussion

Gemcitabine has been commonly employed as the standard chemotherapeutic agent for the treatment of advanced

Table 3 Toxicity of treatment

	NCI-CTC ^b grade (%)			
	1	2	3	4
Hematologic^a (N=50)				
Anemia	31 (62)	13 (26)		
Neutropenia	13 (26)	5 (10)	2 (4)	3 (6)
Thrombocytopenia	13 (26)	2 (4)		
Non-hematologic^b (N=14)				
Nausea			1 (7)	
Diarrhea			2 (14)	
AST/ALT	2 (14)			
Neuropathy	1 (7)			

^a Per cycle

^b Per person, maximum toxicity of each patient

NCI-CTC National Cancer Institute-Common Toxicity Criteria v3.0, AST Aspartic acid transaminase, ALT Alanine aminotransferase

Table 4 Clinical trials in the salvage treatment of pancreatic cancer

Study	Regimen	Status of treatment	No.	RR (%)	TTP (months)	OS (months)
Cantore [22]	Irinotecan/oxaliplatin	Pretreated	30	10	4.1	5.9
Ulrich-Pur [23]	Raltitrexed/irinotecan	Gemcitabine-refractory	19	16	4.0	6.5
Reni [24]	Raltitrexed/oxaliplatin	Gemcitabine-refractory	41	24	NA	5.2
Ignatiadis [25]	Docetaxel/gefitinib	Gemcitabine-refractory	26	19	2.1	2.9
Tsavaris [21]	Oxaliplatin/LV/5-FU	Gemcitabine-refractory	30	23	5.2	6.2
Yi [26]	Irinotecan	Gemcitabine-refractory	33	9	2.0	6.6
Burris [27]	Rubitecan	Pretreated	43	7	2.0	3.0
Oettle [28]	Oxaliplatin/LV/5-FU	Gemcitabine-refractory	23	NR	NR	5.2
Oh [this study]	Irinotecan/oxaliplatin	Gemcitabine and 5-FU refractory	14	21	1.4	4.1

RR response rate, TTP time to progression, OS overall survival, LV leucovorin, 5-FU 5-fluorouracil, NR not reported

pancreatic cancer [1]. 5-FU is also extensively utilized as an adjuvant chemotherapy, a chemoradiotherapeutic agent for patients with locally advanced pancreatic cancer, and a gemcitabine-combined or gemcitabine-refractory salvage chemotherapy in cases of metastatic pancreatic cancer [17–21]. However, the low response rate and early disease progression are requirements for the salvage treatment of pancreatic cancer. Several candidate agents—irinotecan, oxaliplatin, docetaxel, gefitinib, raltitrexed, and rubitecan—have been assessed for their possible efficacy as a second-line therapy for patients who refractory to gemcitabine (Table 4) [21–27]. There is, however, no consensus regarding second-line therapy for patients with gemcitabine refractory disease. Furthermore, it is questionable that salvage chemotherapy for patients with advanced pancreatic cancer will result in prolonged survival, and there remains some potential for toxicity from the treatment. In a randomized phase III trial after the failure of first-line gemcitabine, BSC plus with biweekly oxaliplatin combined with weekly 5-FU as a 24-hour infusion plus leucovorin (OFF) was compared to BSC alone. After 46 patients out of 165 planned, the BSC arm had to be closed because BSC alone was no longer accepted by participating center, with a possible survival benefit for second-line chemotherapy (21 weeks in OFF group versus 10 weeks in BSC group) [28]. After this, preliminary data from a clinical trial in which OFF was randomly compared with 5-FU/leucovorin provided the first evidence for a possible survival benefit associated with the use of oxaliplatin in a second-line setting. Irinotecan monotherapy or combination with other drugs has also been shown to be marginally effective and well tolerated in gemcitabine refractory second-line treatment.

Combined irinotecan and oxaliplatin treatment in patients pre-treated with advanced pancreatic cancer evidenced a response rate of 10% and overall survival duration of 5.9 months [22].

In our study, the overall response and disease control rates were 21.4% and 50%, respectively. Even though all patients were refractory to gemcitabine and 5-FU, this response rate was comparable to previous second-line trials— which were concerned principally with gemcitabine refractoriness. However, time to progression and overall survival duration (1.4 months and 4.1 months) were slightly shorter than has been reported in other studies. This may be because eight out of 14 patients (57%) were treated with IROX as a third-line treatment, and 28.6% of patients had poor performance status (ECOG 2). Performance status of patients has been a crucial role to determine whether to receive salvage treatment or not. In our data, patients with performance status of ECOG 1 had tendency to have longer survival duration than ECOG 2 (5.1 month versus 1.5 months, $P=0.077$).

The dosages of the irinotecan and oxaliplatin administered in our study were somewhat higher than in IROX

regimens that had been utilized in the treatment of colorectal cancer (oxaliplatin 85 mg/m² and irinotecan 200 mg/m² on day 1 administered every 3 weeks) and non-small cell lung cancer (oxaliplatin 130 mg/m² day 1 and irinotecan 65 mg/m² on day 1 and day 8 every 3 weeks) [29, 30]. However, hematologic and non-hematologic toxicities were not increased as compared with those reports, and these effects are manageable with symptomatic supportive care.

The results of this exploratory study demonstrate that the IROX regimen appears to constitute a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who had been previously treated with gemcitabine- and 5-FU-based chemotherapy. Further exploration into IROX combination treatment for patients with gemcitabine- and 5-FU- refractory pancreatic cancer is clearly warranted.

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