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ORIGINAL ARTICLE

Gemcitabine and oxaliplatin combination as first-line treatment for advanced pancreatic cancer: a multicenter phase II study

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Abstract
Purpose Gemcitabine is the only drug approved for single-agent therapy in advanced pancreatic carcinoma (APC). Gemcitabine-based combination chemotherapy has not yet shown promising results.
Methods This multicenter phase II study enrolled previously untreated patients with locally advanced and/or metastatic pancreatic adenocarcinoma. Patients received 1,000 mg/m^2 gemcitabine, 100-min infusion, day 1 and 100 mg/m^2 oxaliplatin, 2-h infusion, day 2; q2w. The primary end point was response rate (RR).
Results Thirteen study centers enrolled 48 eligible patients of which 44 were evaluable. The RR, median overall survival, and median time to progression were 18.2%, 9.4 and 5.6 months, respectively. Sixteen patients (36.4%) experienced clinical benefit. The global quality of life scores improved by 11.71. Grade 3/4 peripheral sensory neuropathy was noted (2.1%), while the most common hematologic toxicity was anemia (grade 3/4, 6.3%).
Conclusions Gemcitabine and oxaliplatin combination chemotherapy showed a promising activity in APC patients and was well tolerated.

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Keywords Advanced pancreatic cancer · Combination chemotherapy · Gemcitabine · GEMOX · Oxaliplatin

Introduction

Pancreatic cancer continues to be a clinical challenge despite the advances in our understanding of its molecular and genetic basis. Gemcitabine is the first therapeutic agent for pancreatic cancer which demonstrated benefits in terms of survival and improvement of disease-related symptoms in a randomized clinical trial [1]. Patients treated with gemcitabine had a median survival of 5.7 months as compared to 4.4 months in those treated with fluorouracil. Furthermore, 25% patients on gemcitabine therapy were alive at 9 months when compared with 6% patients on fluorouracil therapy. Therefore, gemcitabine single-agent chemotherapy is currently considered the standard of care for patients with advanced pancreatic cancer (APC) and serves as the reference regimen in recently published trials [2, 3]. However, it is associated with poor outcome and requires urgent improvement, as suggested by recently reported studies on gemcitabine-based combination therapy including gemcitabine/cisplatin or gemcitabine/fluorouracil for pancreatic cancer [4, 5]. Gemcitabine showed synergistic activity with cisplatin in preclinical studies [6, 7], and the combination was superior to gemcitabine single-agent chemotherapy in terms of time to progression (TTP) [8, 9].

Oxaliplatin is a novel platinum derivative in which the platinum atom is complexed with a 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group. Although the mechanism of action of oxaliplatin is similar to that of cisplatin in terms of types and percentages of DNA-platinum (DNA-Pt) adducts formed, pre-clinical studies suggested that oxaliplatin possessed several unique attributes related to its cytotoxic/antitumoral activity as compared to cisplatin. Oxaliplatin DNA-Pt adducts are bulkier and more hydrophobic than cisplatin DNA-Pt adducts and may be more effective in inhibiting DNA synthesis [10–13]. DNA mismatch repair complexes do not recognize DACH-platinum (DACH-Pt) adducts of oxaliplatin [14, 15]. Experimental data on naked and intracellular DNA suggest that oxaliplatin DNA-Pt adducts have a higher cytotoxic efficacy than cisplatin DNA-Pt adducts [10, 11]. Thus, oxaliplatin is more potent than cisplatin against many tumor cell lines, including different pancreatic cancer cell lines resistant to cisplatin and carboplatin [16, 17].

Based on the above data, we designed this study to evaluate the efficacy and tolerability of gemcitabine plus oxaliplatin (GEMOX) in patients with locally advanced or metastatic pancreatic cancer.

Materials and methods

Patient selection

This study was approved by the institutional review boards of the individual study centers. Written informed consent was obtained from all patients prior to initiation of therapy. This study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

The study enrolled patients with unresectable, pathologically proven, locally advanced or metastatic adenocarcinoma of the exocrine pancreas. Primary radiotherapy along with adjuvant therapy was allowed, except at the target site. Other eligibility criteria included measurable disease, age between 18 and 75 years, Karnofsky performance status (KPS) $\geq$60%, no previous chemotherapy, no clinical signs of central nervous system (CNS) involvement, no previous peripheral neuropathy, life expectancy $\geq$12 weeks, adequate biological parameters (neutrophil count, >1,500/mL; platelet count, >100,000/mL; alkaline phosphatase, $\leq$5$\times$ the institutional upper limits of normal [ULN]; aspartate aminotransferase [AST] and alanine aminotransferase [ALT], $\leq$2.5$\times$ ULN without liver metastasis or $\leq$5$\times$ ULN with liver metastasis; creatinine, $\leq$1.5$\times$ ULN; and bilirubin, $\leq$1.5$\times$ ULN), and a negative pregnancy test for women of childbearing age. Exclusion criteria included pregnancy or lactation, uncontrolled infection, chronic debilitating disease, CNS metastasis, corticosteroid use (except as an antiemetic), uncontrolled and sustained hypercalcemia, Vater's ampuloma, and biliary tract adenocarcinoma.

Treatment plan and dose adaptation

Each treatment cycle consisted of a 100-min intravenous (i.v.) infusion of 1,000 mg/m^2 gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) in 500 ml normal saline on day 1 and a 2-h i.v. infusion of 100 mg/m^2 oxaliplatin (Eloxatin; sanofi-aventis, Paris, France) in 500 ml of 5% dextrose on day 2. The treatment cycles were repeated every 2 weeks.

Dose reduction was based on the worst toxicity observed during the previous cycle. In case of grade 3/4 non-neurologic toxicity, the subsequent cycle was administered after recovery, with the gemcitabine dose decreased to 800 mg/m^2 (80-min infusion) and the oxaliplatin dose decreased to 85 mg/m^2 (2-h infusion). The oxaliplatin dose was reduced to 85 mg/m^2 or temporarily discontinued in case of grade 2 peripheral sensory neuropathy. The patients continued to receive gemcitabine monotherapy according to the same biweekly schedule until recovery to grade 1 neuropathy. If further symptoms occurred during subsequent cycles, the treatment was stopped. All patients received chemotherapy until disease progression, patient refusal, or unacceptable toxicity.

Pretreatment and follow-up evaluation

The medical history was recorded and the physical examination was performed before enrollment and before each chemotherapy cycle. An electrocardiogram, chest X-ray, and biological analyses (complete blood count, serum creatinine, bilirubin, AST, ALT, alkaline phosphatase, and CA 19-9 level) were performed during the 2-week interval preceding the initiation of treatment. Tumor measurement by computed tomography (CT) was performed within 21 days of the start of treatment. During the treatment period, blood counts, toxicity evaluation, and physical examination were performed before each chemotherapy cycle, and the performance status, weight, pain assessment on a visual analog scale, and analgesic consumption (to evaluate clinical benefits) were monitored before each chemotherapy cycle.

Tumor assessment by the same imaging method was done after every four chemotherapy cycles, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Objective responses were confirmed by imaging after 1 month. Tumor response was assessed by the investigators and reviewed by an independent review committee (IRC).

For follow-up examination, abdominopelvic CT scan was performed in case of metastatic lesions of the liver and other abdominal organs (such as the adrenal gland, common bile duct, ureter, omentum, spleen, lymph nodes, and peritoneum), while chest CT scan was performed in patients with lung metastasis. At the end of four chemotherapy cycles, each patient was categorized according to one of the following outcomes: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), early progression, and death from any cause. TTP was calculated from the first treatment infusion to the first objective evidence of disease progression, as assessed by CT scan. Overall survival (OS) was measured from the initial treatment to death.

Clinical benefit was evaluated according to the Andersen and Rothenberg definition [18]. Patients with less pain ($\geq$50% improvement from baseline) on the visual analog scale, decreased analgesic consumption ($\geq$50% reduction compared with baseline consumption), or improved KPS ($\geq$20 points compared with baseline evaluation) without worsening of any of these parameters for at least four consecutive weeks were considered as having a clinical benefit. Patients stable on both the primary measures of clinical benefit (pain and KPS) were then classified as either responders (weight gain $\geq$7% from baseline sustained for $\geq$4 weeks) or nonresponders.

Quality of life (QOL) was assessed with the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire (QLQ)-C30 version 3.0—30-item questionnaire that includes five functional scales, three symptom scales, one QOL scale, and six single items on common symptoms [19–21]. The questionnaires were distributed to the patients before treatment and after two treatment cycles. The questionnaires were scored according to the EORTC instructions. Baseline and last available responses were compared. The primary outcome was the change in global QOL, and the secondary outcomes were changes in physical, role, emotional, cognitive, and social functions.

Adverse event reporting was performed with the National Cancer Institute-Common Toxicity Criteria (version 3.0). Toxicity was evaluated before each treatment cycle. The maximum grade of each type of toxicity was recorded for each patient, and frequency tables were used to determine the toxicity patterns. If toxicity persisted after the termination of chemotherapy, the patient was followed-up until full recovery from the toxicity. When feasible, such patients were followed-up at 3-month intervals until death.

Statistical analysis

Fleming's single-stage design [22] was used for sample size determination with an inactivity cut-off of 15% and an activity cut-off of 30%. Hence, the null hypothesis H_0 was $r \leq 15\%$ and the alternative hypothesis H_A was $r \geq 30\%$, where r was the response rate (RR). The type I error (α) was 0.05 (one-sided), and the type II error (β) was set to 0.2 with 80% power. The sample size was determined to be 43 patients. Assuming that approximately 10% patients would be unevaluable, 48 patients would have to be enrolled in this study. Log-rank tests and Kaplan–Meier estimations were performed for analyzing TTP and OS. Objective response and clinical benefit were calculated with 95% confidence intervals (CIs). When suitable, χ^2 or Fisher's exact test were used to compare qualitative data. Differences were assumed to be statistically significant at $P < 0.05$.

Results

Patient characteristics

Between August 2005 and September 2006, the study enrolled 48 patients of which 44 were considered evaluable. The intention-to-treat (ITT) population comprised 48 patients who received treatment, while the per protocol (PP) population comprised 44 patients. The enrolled patients included 29 men and 19 women, with a median age of 60 years (range, 36–75 years) (Table 1). Twelve patients (25%) had locally advanced disease, while 36 (75%) had metastatic disease. Six patients (12.5%) had previously undergone surgery but had received no prior chemotherapy or radiotherapy. The majority of patients had KPS $\geq$80 (KPS 80–90, 77.1%; KPS 100, 6.3%).

Table 1 Baseline characteristics

	ITT population	PP population
Number of patients	48	44
Age (years)		
Median	58.0	60.0
Minimum/maximum	36/75	36/75
Sex [*n* (%)]		
Male	29 (60.4)	28 (63.6)
Female	19 (39.6)	16 (36.4)
KPS score [*n* (%)]		
60	2 (4.2)	2 (4.6)
70	6 (12.5)	5 (11.4)
80	25 (52.1)	24 (54.6)
90	12 (25)	10 (22.7)
100	3 (6.3)	3 (6.8)
Disease status [*n* (%)]		
Locally advanced	12 (25)	12 (27.3)
Metastatic	36 (75)	32 (72.7)
Metastasis site [*n* (%)]		
Liver	25 (52.1)	23 (52.3)
Lung	2 (4.2)	2 (4.6)
Other	15 (47.9)	20 (45.5)
Prior surgical resection [*n* (%)]	6 (12.5)	5 (11.4)

ITT intention-to-treat, *PP* per protocol, *KPS* Karnofsky performance status

Outcomes

Efficacy was determined by evaluating the tumor response, clinical benefit, and survival data (Table 2). Of the 48 treated patients, four had tumors that were not assessed. The remaining 44 patients were evaluable for response and clinical benefit. A positive response was observed in eight patients (CR, nil; PR, 8 patients); the overall RR was 18.2%, as confirmed by the investigators. However, the IRC review reported a positive response (CR or PR) in 12 patients (RR of 27.3%). With a median follow-up of 124 days, the median TTP and OS in the treated population were 5.6 months (Fig. 1) and 9.4 months (Fig. 2), respectively.

Dose intensity

A total of 336 treatment cycles were administered (median 7; range 1–15). The planned gemcitabine and oxaliplatin dose intensities were 456.34 mg/m^2 per week and 45.97 mg/m^2 per week, respectively. The administered gemcitabine and oxaliplatin dose intensities for all cycles were 91 and 92% of the planned dose intensities, respectively. Four patients (8.4%) discontinued oxaliplatin treatment [peripheral neuropathy in three patients (3.6%) and hypersensitivity reaction in one patient (2.1%)]. Frequency of dose reductions by cycle is shown in Table 3.

Quality of life

Forty-four patients completed the EORTC QLQ-C30 questionnaire. In terms of the primary QOL endpoint, global QOL scores improved by 11.7 points (Table 4). The physical, role, emotional, cognitive, and social functions, which were the secondary QOL endpoints, improved by 3.2, 7.5, 8.5, 1.6, and 9.1 points, respectively. The scores of fatigue, nausea, and vomiting decreased by 3.7, 1.2, and 13.9 points, respectively, indicating fewer symptoms. Changes in global QOL scores were not associated with treatment response or median survival (data not shown).

Toxicity

Seven chemotherapy cycles were administered every 2 weeks. All 48 treated patients were assessed for safety

Table 2 Response rate, clinical benefit response, and survival data

Efficacy parameter	Locally advanced disease (*n* = 12)	Metastatic disease (*n* = 36)	Overall (*n* = 48)
Response (*n*)			
Complete response	0	0	0
Partial response	2	6	8
Stable disease	7	12	19
Progression	3	14	17
Not Done	0	4	4
Response rate (%)	16.7	18.8	18.2
Clinical benefit [*n* (%)]			
Assessable	12 (27.3)	32 (72.7)	44 (100.0)
Response	5 (41.7)	11 (30.6)	16 (36.4)
Median TTP (months)	9.2	4.0	5.6
Median OS (months)	–	7.4	9.4

TTP time to progression, *OS* overall survival

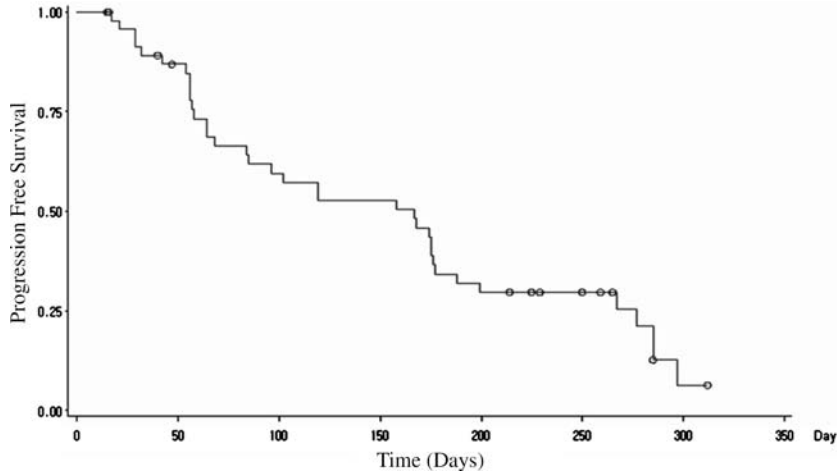

Fig. 1 Time to progression in patients receiving gemcitabine and oxaliplatin for metastatic pancreatic adenocarcinoma

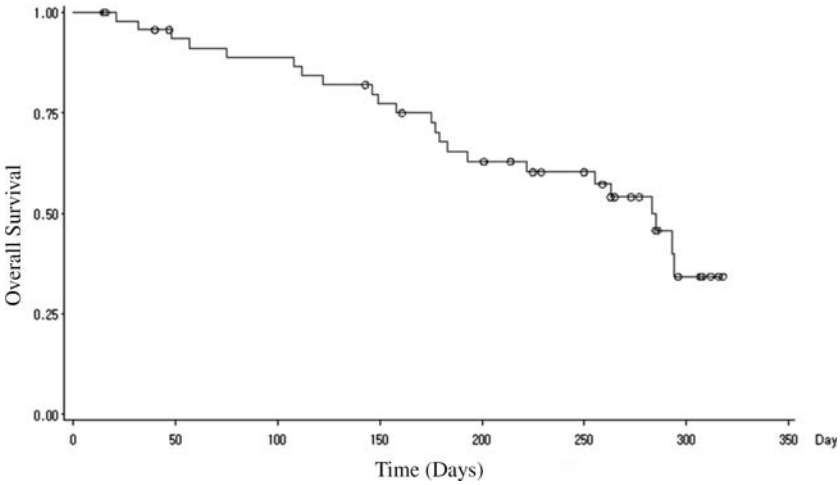

Fig. 2 Overall survival in patients receiving gemcitabine and oxaliplatin for metastatic pancreatic adenocarcinoma

(Table 5). Grade 3/4 hematologic toxicities included anemia in three patients (6.3%), neutropenia in three patients (6.3%), and thrombocytopenia in one patient (2.1%). Gastrointestinal toxicity was the most prevalent among non-hematologic toxicities. Grade 3 gastrointestinal toxicities included nausea in two patients (4.2%), vomiting in two patients (4.2%), and diarrhea in one patient (2.1%). Grade 3/4 peripheral neuropathy was noted in one patient (2.1%). Four deaths occurred in patients not responding to therapy; these deaths were considered unrelated to study treatment.

Discussion

The present study is the first to report the efficacy and safety of the GEMOX combination therapy (1,000 mg/m^2 gemcitabine and 100 mg/m^2 oxaliplatin) in Korean patients with APC. It demonstrated the longest median OS (9.4 months) reported in Korean patients with APC till date, which is reflective of efficacy of GEMOX. Earlier studies conducted in Korean APC patients have reported median OS ranging from 3.6 to 7.2 months [23–27].

In many phase II studies, gemcitabine combinations improved the RR and OS [28]. Based on these results, many prospective randomized phase III trials compared gemcitabine-based combination regimens with gemcitabine alone; however, these studies yielded varying results and included a small number of patients. In a meta-analysis of 22 randomized controlled trials, Xie et al. [29] showed that compared with gemcitabine monotherapy, gemcitabine-based combination therapy may improve the OS and palliation in optimal APC patients.

Several administration schedules can potentially improve the activity of gemcitabine-based combination chemotherapy. French investigators showed that 1,000 mg/m^2 gemcitabine (dosage, 10 mg/min/m^2) plus 100 mg/m^2 oxaliplatin administered every 2 weeks resulted in a median PFS of 5.3 months and a better median OS of 9.2 months, with 36% patients remaining alive at 1 year [30]. These results have been confirmed by a phase III randomized study comparing GEMOX with gemcitabine alone (1,000 mg/m^2 by a weekly 30-min i.v. infusion) in which GEMOX therapy resulted in a better RR (26.8 vs. 17.3%, $P = 0.4$) and median OS (9.0 vs. 7.1 months, $P = 0.13$) [9].

Table 3 Frequency of dose reduction in patients receiving oxaliplatin and gemcitabine for pancreatic adenocarcinoma

Cycle no.	No. of patients treated	Oxaliplatin		Gemcitabine	
		Full dose [*n* (%)]	Reduced dose [*n* (%)]	Full dose, [*n* (%)]	Reduced dose [*n* (%)]
1	48	48 (100.0)	0 (0.0)	48 (100.0)	0 (0.0)
2	42	39 (92.9)	3 (7.1)	40 (95.2)	2 (4.8)
3	39	37 (94.9)	2 (5.1)	37 (94.9)	2 (5.1)
4	38	37 (97.4)	1 (2.6)	37 (97.4)	1 (2.6)
5	28	26 (92.9)	2 (7.1)	27 (96.4)	1 (3.6)
6	27	27 (100.0)	0 (0.0)	27 (100.0)	0 (0.0)
7	24	24 (100.0)	0 (0.0)	24 (100.0)	0 (0.0)
8	22	22 (100.0)	0 (0.0)	22 (100.0)	0 (0.0)
9	18	18 (100.0)	0 (0.0)	18 (100.0)	0 (0.0)
10	16	13 (81.3)	3 (18.8)	14 (87.5)	2 (12.5)
11	13	13 (100.0)	0 (0.0)	13 (100.0)	0 (0.0)
12	11	10 (90.9)	1 (9.1)	11 (100.0)	0 (0.0)
13	5	5 (100.0)	0 (0.0)	5 (100.0)	0 (0.0)
14	2	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)
15	2	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)
16	1	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)

Table 4 Changes in QOL scores from baseline to last known values ($N = 44$)

Scale	Baseline score	Best score after treatment	Change (best score–baseline score)
Global QOL	50.60 ± 22.94	62.30 ± 17.77	11.71 ± 22.70
Function			
Physical	73.81 ± 19.61	76.98 ± 16.28	3.17 ± 15.39
Role	68.65 ± 27.60	76.19 ± 23.03	7.54 ± 33.78
Emotional	71.83 ± 19.99	80.36 ± 23.49	8.53 ± 24.10
Cognitive	84.92 ± 14.64	86.51 ± 19.90	1.59 ± 22.63
Social	63.10 ± 24.84	72.22 ± 26.97	9.13 ± 26.08
Symptom			
Fatigue	38.62 ± 21.43	34.92 ± 22.70	3.70 ± 22.85
Nausea and vomiting	15.48 ± 23.68	14.29 ± 20.35	1.19 ± 24.53
Pain	37.70 ± 28.05	23.81 ± 25.80	13.89 ± 29.66

All values are mean ± SD
QOL quality of life

Another study reported median OS of 4.96, 6.01, and 6.47 months with gemcitabine alone (1,000 mg/m^2 by a weekly 30-min i.v. infusion), fixed dose rate (FDR) gemcitabine alone (1,500 mg/m^2 by a weekly 150-min i.v. infusion), and GEMOX, respectively [31].

The North Central Cancer Treatment Group's phase II study that included 47 patients with previously untreated APC and used a different GEMOX regimen (100 mg/m^2 oxaliplatin on day 1 and 1,000 mg/m^2 gemcitabine as a 30-min i.v. infusion on days 1 and 8 of a 3-week cycle) showed a limited benefit from the addition of oxaliplatin to gemcitabine. In that study, 50% patients survived ≥6 months; the median TTP was 4.5 months; and the median duration of response was 2.7 months [32]. Based on other phase I studies employing a gemcitabine/oxaliplatin combination chemotherapy [30, 33–35], the present chemotherapy schedule involved the administration of 1,000 mg/m^2 gemcitabine on day 1 and 100 mg/m^2 oxaliplatin on day 2. However, Airoldi et al. [36] found no sequence-dependent pharmacokinetic interaction while comparing gemcitabine–oxaliplatin versus oxaliplatin–gemcitabine combination therapy in APC patients. We think that the limited benefit obtained from the combination chemotherapy may be attributed to the method of gemcitabine administration, but this remains to be confirmed.

Pharmacokinetic studies of gemcitabine suggest that a higher intracellular level of the active metabolite is achieved with an FDR infusion of 10 mg/m^2 per minute than with the standard 30-min infusion [37, 38]. In a phase II randomized trial of these two approaches, the FDR

Table 5 Most common treatment-related adverse events (NCI–CTC) ($N = 48$)

Adverse events	Grade 1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Hematologic				
Anemia	23 (47.9)	18 (37.5)	2 (4.2)	1 (2.1)
Leucopenia	11 (22.9)	4 (8.3)	–	–
Neutropenia	1 (2.1)	4 (8.3)	3 (6.3)	–
Thrombocytopenia	28 (58.3)	1 (2.1)	1 (2.1)	–
Non-hematologic				
Bilirubin	3 (6.3)	1 (2.1)	6 (12.5)	–
AST/ALT	27 (56.3)/24 (50)	5 (10.4)/9 (18.8)	1 (2.1)/1 (2.1)	–
Alkaline Phosphatase	19 (39.6)	10 (20.8)	1 (2.1)	–
Nausea	21 (43.8)	15 (31.3)	2 (4.2)	–
Vomiting	12 (25.0)	15 (31.3)	2 (4.2)	–
Diarrhea	8 (16.7)	2 (4.2)	1 (2.1)	–
Anorexia	15 (31.3)	13 (27.1)	1 (2.1)	–
Edema	3 (6.3)	–	–	–
Dyspnea	–	1 (2.1)	–	–
Sensory neuropathy	8 (16.7)	1 (2.1)	1 (2.1)	–
Fatigue	8 (16.7)	4 (8.3)	2 (4.2)	–
Fever	4 (8.3)	2 (8.3)	–	–
Infection	–	1 (2.1)	–	–
Hemorrhage/bleeding	–	–	–	–
Alopecia	7(14.6)	2 (4.2)	–	–

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *NCI–CTC* National Cancer Institute Common Toxicity Criteria

infusion yielded more promising results [39]. With our fixed-dose infusion design, we observed an OS similar to that in the GERCOR data [30], but the RRs differed. Although our overall investigator-confirmed RR was 18.2%, the IRC review yielded a RR of 27.3%. These differences were probably related to inter-observer variations in the measurements of tumor size at baseline and follow-up CT scans. In patients with locally advanced tumors, tumor margin differentiation is difficult and may lead to variations in tumor size measurements. Moreover, in patients with multiple lesions, different target lesions might have been selected by the investigators and IRC members. Such differences in investigator- and IRC-reported RRs are also found in other studies. In a study on sorafenib treatment for advanced renal cell carcinoma, Escudier et al. [40] reported partial RRs of 2 and 10%, as assessed by the IRC and investigators, respectively. In another study on docetaxel chemotherapy for metastatic breast cancer, the RRs reported by the investigators and IRC ranged between 38 and 28% [41].

While most of the earlier trials on pancreatic cancer assessed only the clinical benefit (pain, performance status, and weigh gain) but not the QOL, the present trial is one of the few studies in which the QOL was measured with an internationally validated tool. Few studies have demonstrated an improvement in the QOL with chemotherapy. Glimelius et al. [20] randomly assigned 53 patients to chemotherapy plus best supportive care (BSC) or BSC alone and showed that 38% patients in the chemotherapy group were considered to have a favorable QOL outcome compared with only 13% in the BSC group. Two other studies formally assessed the QOL during gemcitabine treatment; one study reported an improvement in the QOL while the other reported a worsening of the QOL at 4 and 8 weeks [42, 43]. The QOL can be greatly decreased by the side effects of chemotherapy or symptoms of APC. However, in our study, the EORTC QLQ-C30 global and functional scales yielded improved scores after treatment. A greater improvement in median scores was observed in the case of pain symptoms and global scales. Conroy et al. [44] reported that responders experienced major improvements in the global QOL, but we did not observe such improvements in our study. Evaluation of the clinical benefit is also very important. Burris et al. [1] reported that meaningful effects on disease-related variables such as pain control, performance status, and weight gain were seen in 23.8% patients in the gemcitabine-only group, while Louvet et al. [9] observed clinical benefit in 38.2% patients in the GEMOX group. This finding was similar to our result of 36.4% patients experiencing a clinical benefit.

A favorable toxicity profile is a major attribute for a chemotherapeutic agent administered to fragile patients in the palliative setting. In our study, less than 5% patients on GEMOX therapy experienced grade 4 overall toxicities. Only

10% patients experienced grade 3/4 hematologic toxicity, and 2.1% patients experienced grade 3/4 sensory neuropathy. The toxicity profile of GEMOX was found to be very acceptable, manageable, and of limited clinical significance.

This study provides evidence that GEMOX is a reasonable and appropriate first-line gemcitabine-based treatment option for APC patients. A potential approach to further improving the beneficial effects of GEMOX in APC patients would be to conduct a pharmacokinetic study aimed at optimizing drug delivery. We suggest that a phase III clinical trial be conducted to clarify both the benefit of an FDR infusion of gemcitabine in GEMOX combination and the added value offered by oxaliplatin.

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