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ORIGINAL ARTICLE

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# Gemcitabine plus celecoxib (GECO) in advanced pancreatic cancer: a phase II trial

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**Abstract** *Introduction*: Single agent gemcitabine (GEM) is the standard treatment of pancreatic adenocarcinoma. Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor. Recent studies in human pancreatic tumor cell lines suggest an involvement of COX-2 in tumor-dependent angiogenesis and provide the rational for inhibition of the COX pathway as an effective therapeutic approach. The aim of this study is to evaluate the toxicity and activity of gemcitabine plus celecoxib. *Patients and methods*: Forty-two consecutive patients with histologically or cytologically confirmed pancreatic adenocarcinoma entered the trial. Twenty-six patients (pts) were metastatic, 16 pts had locally advanced disease. The schedule consisted of GEM 1,000 mg/m$^2$ (as a 30 min iv infusion) on days 1, 8 every 3 weeks and celecoxib 400 mg bid. *Results*: Four pts (9%) achieved a partial response and 26 (62%) had stable disease, gaining a total disease control in 30 pts (71% [95% CI, 58–84%]). Overall clinical benefit response was experienced by 23 pts (54.7% [95%CI, 38.6–70.1%]). Neither grade 4 neutropenia nor grade 3–4 thrombocytopenia was observed. Grade 3 neutropenia was detected in 19% of pts. Grade 3 non-hematological toxicity was as follows: hepatic toxicity 7%, nausea 2.3%. Three pts (7%) and 5 pts (12%) had respectively a minimum creatinine increase and edema. Median survival was 9.1 months (95% CI, 7.5–10.6 months). *Conclusion*: GEM in combination with celecoxib showed low toxicity, good clinical benefit rate and good disease control. Further clinical investigation is warranted.

**Keywords** Gemcitabine · Celecoxib · Pancreatic cancer

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## Introduction

Pancreatic adenocarcinoma persists to be an unsolved health problem, with approximately 30,000 deaths per year in the United States and 50,000 deaths per year in Europe [1]. Cancer of the exocrine pancreas is the fourth principal cause of cancer-related death for both men and women and it is associated with the lowest survival rate of any major cancer type. The frequent diagnosis at advanced stages, the aggressiveness of pancreatic cancers, and its chemoresistance, lead to a median survival of 6 months in patients with advanced disease.

Gemcitabine represents the standard chemotherapy for the advanced disease, gaining a significant improvement in clinical benefit and overall survival as measured up to fluorouracil [2]. In phase III trials, gemcitabine-based combination schedules with antimetabolites, cisplatin and its analogues, have failed to demonstrate the superiority in terms of survival as compared with gemcitabine alone.

Being the actual chemotherapeutic agents that are unsatisfactory in the systemic treatment of metastatic disease, the study of novel targeted drugs based on the evolving understanding of the molecular biology of pancreatic cancer must receive the highest priority. Different areas of clinical investigation may yield encouraging results. These include interruption or modulation of known growth factors and signal transduction pathways involved with cell growth, invasion, and angiogenesis. The recent discoveries about molecular events in pancreatic cancerogenesis concern the

accumulation of multiple genetic and epigenetic changes, including inactivation of tumor-suppressor genes and activation of proto-oncogenes. Based on the frequency with which mutations in K-ras, p53, and p16 are found, a model of pancreatic carcinogenesis has been suggested whereby the malignant clone evolves from cells driven by a dominant oncogene (K-ras) with subsequent deregulation of cell growth precipitated by abnormal cell-cycle control resulting from mutations in p53, p16, or both [3]. Close to the genetic mutations, the overexpression of matrix metalloproteinases, growth factors and their receptors contribute to the intricate oncogenesis of pancreatic cancer. Besides, research suggests that the COX-2 enzyme is overexpressed in a broad range of premalignant, malignant, and metastatic human epithelial cancers, including pancreatic adenocarcinoma. In the latter, the COX-2 protein was detected in 90% of cases [4]. The COX-2 enzyme is also expressed in existing and angiogenic vasculature within and adjacent to hyperplastic/neoplastic lesions [5]. In addition to the well-established pathophysiological role that COX-2 plays in inflammation, recent evidence implies that this isoform may also be involved in multiple biologic events throughout the tumorigenic process. Current evidence indicates that COX-2 promotes tumor-specific angiogenesis, inhibits apoptosis via Bcl-2 expression and Akt signaling, and induces proangiogenic factors such as VEGF, inducible nitrogen oxide synthetase promoter (iNOS), IL-6, IL-8, and TIE-2 [6–8]. COX-2-derived metabolites from infiltrating inflammatory cells contribute to the tumorigenic process as well. In particular, COX-2-induced prostaglandin E2 (PGE2) increases intracellular cAMP, in turn stimulating VEGF production and thereby promoting neovascularization and tumor angiogenesis [9]. Besides, constitutive COX-2 expression leads to enhanced cell migration and invasiveness. The biochemical changes associated with the overexpression of COX-2 include increased expression and activation of metalloproteinase-2 and reduced expression of E-cadherin [10]. The effects of COX inhibition on pancreatic cancer growth has been examined in vitro and in vivo, using both non-specific NSAIDs and specific COX-2 inhibitors, such as celecoxib. These studies demonstrate that COX inhibitors significantly induce apoptosis in pancreatic cancer cells [11], decrease both volume and weight of pancreatic tumors xenografted subcutaneously into nude mice and suppress VEGF expression in orthotopic pancreatic cancer animal models, thus inhibiting tumor progression and metastasis [12].

The up-regulation of COX-2 in pancreatic cancer and its involvement in the control of tumor-dependent angiogenesis and growth provide the rationale for the inhibition of the COX-2 pathway as an effective therapeutic approach, as a single modality or in combination with current anticancer agents. For this reason, we evaluated the combination of gemcitabine and a COX-2 inhibitor, celecoxib, in patients with advanced pancreatic adenocarcinoma in a bi-institutional phase II trial. Celecoxib dosage was 400 mg twice daily, as recommended by FDA for prevention of FAP. Considering toxicities reported by Burris [2] with the weekly schedule for 3 weeks of every 4 (grade 3/4 neutropenia 26%, thrombocytopenia 9.7%, anemia 10%, nausea/vomiting 12.7%), and the frail population of patients affected by pancreatic adenocarcinoma, we decided to modify gemcitabine schedule in 1,000 mg/m$^2$ for 2 weeks of every 3. Nevertheless, this schedule permits maintenance of a similar dose intensity (708 vs. 791 mg/m2/w in 24 weeks of treatment).

## Patients and methods

### Patients

Forty-two consecutive pts were enrolled onto this study from January 2002 to December 2003.

Eligibility criteria were as follows: histologically proven locally advanced or metastatic adenocarcinoma of the pancreas; Karnofsky performance status ≥ 50%; no prior palliative chemotherapy or radiotherapy; adequate hematologic function (neutrophil count $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l); adequate renal and hepatic functions (creatinine ≤ 1.25 times the upper limit of normal [ULN], total bilirubin ≤ 1.25 times the ULN, AST and ALT ≤ 3 times the ULN [in cases of liver metastasis, total bilirubin ≤ 1.5 times the ULN, AST and ALT ≤ 5 times the ULN]). All patients were informed of the investigational nature of this study, and each patient provided written informed consent before registration with the study.

### Treatment protocol

Gemcitabine 1,000 mg/m$^2$ was given as a 30-min intravenous (IV) infusion on day 1 and 8, every 3 weeks. Celecoxib was administered orally at a dose of 400 mg bid.

Patients received gemcitabine plus celecoxib until evidence of disease progression, patient refusal, or unacceptable toxicity.

To prevent nausea and vomiting, 5-hydroxytryptamine-3 antagonists intravenously (IV) plus dexamethasone 8 mg IV were administered before chemotherapy.

Patients were assessed for toxicity before each cycle using the National Cancer Institute Common Toxicities Criteria (NCI-CTC, Version 2.0). Treatment was delayed until recovery if neutrophils were less than $1.0 \times 10^9$/l or platelets were less than $75 \times 10^9$/l. Gemcitabine dose was reduced by 25% if grade 2 (NCI-CTC) neutropenia or grade 1 thrombocytopenia. Patients experiencing at least grade 3 non-hematologic toxic effects during a course of therapy were administered 75% of the starting dose for the next cycle. No prophylactic administration of granulocyte colony-stimulating factor

(G-CSF) was allowed. No patients received radiotherapy for localized disease.

### Patient evaluation

Patient pre-treatment evaluation included a detailed medical history and physical examination, performance status assessment, analgesic requirements, complete blood cell count with differential and platelet count, whole blood chemistry, serum levels of CA19.9 and urinalysis. Chest radiograph or computed tomography (CT) scan, abdominal CT scan and/or ultrasound and any other appropriate diagnostic procedure to evaluate metastatic sites were performed within 3 weeks of starting treatment. During treatment, at each visit, physical examination, complete blood cell count, biochemical profile and evaluation of toxicities according to NCI-CTC were performed. At the same time, performance status, weight, pain assessment and analgesic consumption were recorded as well, to evaluate the clinical benefit.

Clinical benefit (CB) was estimated according to Burris' definition [2] on the basis of two primary measures, pain and functional impairment (KPS), and a secondary parameter, body weight change. The pain score was a composite evaluation of pain intensity and analgesic consumption obtained from a daily pain assessment diary completed by the patient. Pain intensity was graded from 0 (least possible pain) to 100 (worst possible pain) on a VAS. Daily analgesic consumption was converted and measured weekly in morphine-equivalent milligrams. Performance status and body weight were assessed by the physician at each study visit. For pain intensity, a positive response occurred when the score was improved by ≥50% from baseline, sustained for ≥4 weeks, assuming a minimum pain score ≥20 on the VAS. For analgesic consumption, a positive response occurred when the weekly consumption was reduced by ≥50% from baseline, maintained for ≥4 weeks, assuming a minimum analgesic consumption ≥10 mg/wk. A positive response for PS was defined as an improvement of ≥20 points from baseline, sustained for at least 4 weeks, for patients with a PS < 80. Any worsening from baseline, sustained for 4 weeks, was considered a negative response for each of the three domains. All the other results were considered stable. A positive weight change was defined as a weight gain (excluding third-space fluid) of ≥7% from baseline, sustained for ≥4 weeks. Pain intensity and analgesic consumption were compared to give a composite pain score. Each patient was classified positive, stable or negative for each of the primary measures (pain and PS). In order to achieve a positive clinical benefit response, patients had to be positive for at least one parameter without being negative for any of the others for a minimum of 4 weeks. Patients who were stable in the two primary measures were classified as stable. These patients could be classified as positive, only if the secondary measure of weight change was classified as positive.

Tumor response was assessed after 4 cycles in accordance with the World Health Organization criteria. In brief, a complete response (CR) was achieved in the case of the disappearance of a clinically assessable disease for at least 4 weeks, and partial response (PR) required at least a 50% reduction of the sum of the products of the perpendicular diameters of all measurable lesions for at least 4 weeks. Progression disease (PD) was described as an increase of at least 25% of the measurable lesions or the appearance of new malignant lesion(s). The remaining patients were considered to have stable disease (SD), if stabilization persisted more than 8 weeks [2]. We defined disease control as the sum of CR + PR + SD.

Time to tumor progression was calculated from the first day of treatment until evidence of clinical progression or tumor progression assessed by CT scan measurement. Survival was measured from the initiation of treatment to the date of death or last contact.

### Statistical analysis

The study was designed as a two-stage, phase II study, with activity as primary end-point. The following parameters were considered for calculation of sample size: 5% as the lower acceptable response rate, 20% as the auspicated response rate, 10% risk of false negative result, 5% risk of false positive result. With these requirements, the study was planned to stop at the first stage if there were no responders among the first 21 pts; otherwise, more patients would be enrolled in the second stage to obtain another 20 assessable pts.

Secondary end-points were clinical benefit rate, toxicity, time to tumor progression (TTP) and overall survival (OS). TTP and OS was estimated by the Kaplan-Meier method [13], and the confidence intervals (CI) for response rate and clinical benefit rate were calculated using methods for exact binomial CIs [14]. The analysis was performed with the SPSS statistics package (version 11.01, SPSS Inc, Chicago, IL).

## Results

### Patients characteristics

A total of 42 pts with advanced pancreatic adenocarcinoma entered the study. The demographic and baseline disease characteristics are listed in Table 1. Median age was 64 years (range, 42–79 years) and Karnofsky performance status was 50–80% in 24 pts (57%).

All patients were assessable for toxicity and response. Four pts experienced a rapid clinical deterioration and died from progressive disease before radiological assessment after the fourth cycle; they were analyzed as having PD at their date of death.

**Table 1** Baseline patient characteristics

| | No. of patients (%) |
|---|---|
| No. of patients | 42 |
| Male/female | 22/20 |
| Age, years | |
| Median | 64 |
| Range | 42–79 |
| Karnofsky performance status | |
| ≥90 | 18 (43) |
| 80–70 | 14 (33) |
| 60–50 | 10 (24) |
| Disease at presentation | |
| Locally advanced | 16 (38) |
| Metastatic | 26 (62) |
| Site of metastatic disease ($n=26$) | |
| Liver | 25 (96) |
| Lung | 3 (7) |
| Ca19.9 at diagnosis | |
| Median | 555 |
| Range | 1–50,000 |
| Baseline pain intensity score | |
| 0–19 | 17 (41) |
| 20–29 | 5 (12) |
| 30–39 | 3 (7) |
| 40–49 | 8 (19) |
| 50–100 | 9 (21) |
| Baseline analgesic consumption (morphine-equivalent mg) | |
| 0–49 | 17 (40) |
| 50–100 | 10 (24) |
| >100 | 15 (36) |

Among the study population, a total of 277 cycles of chemotherapy were administered, with a median number of 6 courses per patient (range, 2–12). Median dose withholding calculated during the entire treatment period was nearly the 95% of planned.

## Treatment efficacy

The objective response data are listed in Table 2. All 42 pts were evaluable for response, according to an intent-to-treat analysis. No CR was observed and four pts (9%) achieved a PR. The overall response rate (RR) was 9% (95% CI, 1–17%). Twenty-six pts (62%) showed stable disease and 12 pts (29%) experienced PD during treatment. The control of disease was attained in 30 pts (71% [95% CI, 58–84%]).

The summary of clinical benefit data in 42 assessable pts are outlined in Fig. 1. For the composite pain score, 21 pts (50%) had a positive response and 16 pts (38%) were classified as stable. Both pain and performance

**Table 2** Response rate

| Response rate | No. of patients (%) | 95% CI |
|---|---|---|
| PR | 4 (9) | 1–17 |
| SD | 26 (62) | 48–76 |
| PD | 12 (29) | 16–42 |
| Disease control (PR + SD) | 30 (71) | 58–84 |

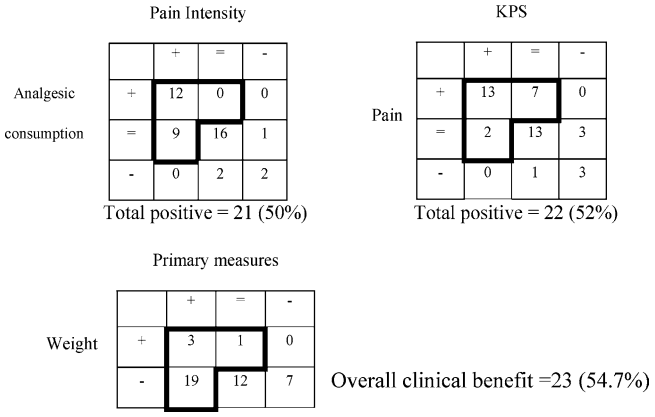


**Fig. 1** Summary of clinical benefit ($n=42$)

status improved in 13 pts, seven pts had an improvement in pain with no worsening of PS, and another two pts had an improvement in PS with stabilization of pain. Consequently, 22 pts (52%) were classified as clinical benefit responders by their primary measures. Considering the secondary measure of clinical benefit, three pts classified as responders by primary measures and one patient categorized as stable by primary measures, had a weight gain of ≥7% during the study. In the final assessment, 23 pts were classified as clinical benefit responders, achieving a clinical benefit response rate of 54.7% (95%CI, 38.6–70.1%). Of note, 16 asymptomatic pts with a KPS > 90% entered the study. Three of them experienced a worsening of KPS and pain during treatment, and they were included in CB assessment as non responders. The other 13 pts remained stable for pain and KPS, and they were classified as stable at CB.

CA19.9 values were recorded at the beginning of chemotherapy and after three cycles. In 18 pts (43%), CA19.9 value was reduced to half after the third cycle and in 13 pts (31%) it was stable.

Median time to tumor progression was 5.1 months (95%CI, 2.9–7.3 months). Median overall survival was 9.1 months (95%CI, 7.5–10.6 months), in the intent-to-treat population.

## Treatment toxicity

All patients were assessable for toxicity. No grade 4 NCI-CTC hematologic and non-hematologic toxicity was observed. The most commonly observed grade 3 adverse events were asymptomatic neutropenia (19%) and hepatic toxicity (7%). Grade 3 and 2 nausea was reported respectively by one patient (2%) and four pts (9.5%). All these toxicities were associated with the administration of gemcitabine. The analyses of celecoxib-related adverse events showed a low toxicity profile. In particular, only grade 1 renal toxicity (7%), heartburn (7%) and edema (12%) were detected. The whole grade 1–4 toxicities are listed in Table 3. Neither toxic death nor life-threatening febrile neutropenia were

**Table 3** Summary of maximum WHO grades for toxicity

| | Grade | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | |
| | No. of patients | % | No. of patients | % | No. of patients | % | No. of patients | % |
| *Gemcitabine-related toxicity* | | | | | | | | |
| Hematologic toxicity | | | | | | | | |
| Neutropenia | 5 | 12 | 12 | 28 | 8 | 19 | – | |
| Thrombocytopenia | 3 | 7 | - | | – | | – | |
| Hb | 4 | 9.5 | 4 | 9.5 | 1 | 2 | – | |
| Non-hematologic toxicity | | | | | | | | |
| Nausea/vomiting | 5 | 12 | 4 | 9,5 | 1 | 2 | – | |
| Hepatic toxicity | 5 | 12 | 8 | 19 | 3 | 7 | – | |
| Mucositis | 4 | 9,5 | 1 | 2 | – | | – | |
| Skin rash | – | | – | | – | | – | |
| *Celecoxib-related toxicity* | | | | | | | | |
| Renal toxicity | 3 | 7 | – | | – | | – | |
| Dyspepsia/heartburn | 3 | 7 | – | | – | | – | |
| Edema | 5 | 12 | – | | – | | – | |

reported. No hospitalization for adverse events occurred and no patients discontinued treatment for toxicity. No celecoxib-related cardiovascular accidents were observed.

## Discussion

COX-2 is overexpressed in a broad spectrum of human malignancies and affects mechanisms implicated in cancerogenesis, such as the enhancement of angiogenesis, the inhibition of apoptosis and the suppression of immune surveillance. Preclinical observations led to study COX-2 specific inhibitors (COXib) in human colorectal cancer cell lines, showing a suppression of tumor growth in cell lines overexpressing COX-2. Preclinical and clinical trials with celecoxib supported the concept that higher doses of COX-2 specific inhibitors may be needed for prevention of cancer than are used to treat inflammation. Steinbach et al. treated familial adenomatous polyposis (FAP) patients with two different dosages of celecoxib (100 or 400 mg twice daily) or placebo, in a double-blind placebo-controlled study [15]. Statistically significant reductions in the number of polyps and in polyp burden were observed in the group treated with 400 mg celecoxib twice daily, compared with the placebo- and 100 mg twice daily-treated groups. On the basis of this study, FDA approved celecoxib as an adjunct to the usual care for FAP patients. From then onwards, other numerous preclinical and clinical trials began to investigate the role of COX-2 inhibitors in the prevention and treatment of different tumors.

Even thought epidemiological studies on the role of COX inhibitors in pancreatic cancer incidence are not as detailed as in colorectal cancer, evidence does suggest that COXib might decrease the incidence of adenocarcinoma of the pancreas. In fact, Anderson et al. investigated the association between pancreatic cancer and non-steroidal anti-inflammatory (NSAIDs) drugs in 28.283 participants. Multivariate analysis suggested that people who used NSAIDs had a 43% lower risk of pancreatic tumor. Epidemiological observations of surrounding areas and in vitro studies demonstrated that COX-2 protein was detected in 90% of pancreatic adenocarcinoma and COX-2 mRNA were more than 60-fold increased in pancreatic cancer in contrast to the adjacent non-tumor tissue [4]. Regulation of COX-2 expression was clearly not due to a mutation in the COX-2 gene. Instead, cancer cell lines and animal tumor models demonstrated that mutation in oncogene k-ras increased COX-2 expression [16], and inactivation of tumor-suppressor gene p53 promoted angiogenesis also via COX-2 induction [17]. Considering the known key role of k-ras and p53 in pancreatic cancerogenesis and their responsibility in COX-2 induction, different authors investigated the meaning of COX-2 inhibition in pancreatic adenocarcinoma, in preclinical studies. The demonstration that celecoxib significantly suppresses proliferation and induce apoptosis in pancreatic cancer cell lines [18] and delay tumor growth and metastasis in xenograft tumor models [19], represents the rationale for using COX-2 inhibitors in the prevention and treatment of pancreatic tumor.

We investigated the therapeutic role of the COX-2 inhibitor, celecoxib, in combination with the standard cytotoxic agent, gemcitabine, in the treatment of metastatic and locally advanced pancreatic adenocarcinoma.

We detected an objective response rate of 9%, even though the accurate assessment of tumor shrinkage in pancreatic cancer is particularly difficult because of the anatomic location of the primary lesion and its associated desmoplastic reaction. On the other hand, patients experienced stable disease in 62%, achieving a control of disease in 71% of cases. This percentage could be explained with the antiangiogenetic and proapoptotic action of COX-2 inhibitor. The inhibition on tumor growth, due to celecoxib antiangiogenic action, results in disease stabilization.

The observed clinical benefit rate (54.7%) is an important goal for the evaluation of this combination regimen. The good CBR could be due in part to the use of a cyclooxygenase inhibitor, which is responsible of the analgesic effect. Nevertheless, this explanation cannot be exhaustive, considering that a mild pain-relieving drug as celecoxib allowed patients to significantly reduce morphine consumption in such a relevant percentage.

Surrounding low toxicity and good clinical benefit response, median overall survival (9.1 months) seems to be an interesting finding. In fact, considering only trials enrolling similar proportion of patients with locally advanced or metastatic disease, in order to have comparable results, we observed a median survival overlapping the ones reported by cytotoxic doublets, such as gemcitabine plus platinum analogues [20–24]. Taking into account that 38% of patients had locally advanced disease and 38% presented a favorable PS, the promising results could be due to the selection of patients with good prognosis. However, in the metastatic group (26 pts), the results were similar (RP = 11%, RP + SD = 77%, OS = 8.9 months).

The results of this study demonstrates that the GECO combination is feasible, active and safe. The efficacy of this regimen, based on the combination of a biological drug and a cytotoxic agent, may be best addressed in a phase III trial, comparing GECO regimen versus gemcitabine alone in patients with advanced pancreatic adenocarcinoma.

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