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Gemcitabine Plus Irinotecan as First-Line Weekly Therapy in Locally Advanced and/or Metastatic Pancreatic Cancer

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Single-agent gemcitabine has been established as standard treatment for advanced pancreatic cancer since clinical studies have shown an improvement in overall survival and significant clinical benefit when compared to the best supportive care despite low overall objective response. Several phase II studies have tested other single agents and different gemcitabine-based regimens in pancreatic cancer, but both response and survival rates have remained low. Irinotecan, a topoisomerase I inhibitor currently approved for the treatment of metastatic colon cancer, has also demonstrated improved response rate in patients with pancreatic cancer. Our purpose was to determine the activity and toxicity of this regimen in patients with unresectable or metastatic pancreatic cancer. Patients with histologically confirmed pancreatic adenocarcinoma received gemcitabine 1000 mg/m^2 plus irinotecan 100 mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle for 6–8 months. From February 2004 to April 2006, 33 patients were entered into this study, 32 of whom were evaluable for treatment response, toxicity, median time to progression, and median survival. Characteristics included a median age of 63 years (range 41–79), 21 males (64%), and 12 females (36%). One patient discontinued treatment due to adverse effects. The total number of cycles administered was 188 and the median number of cycles for patients was 5.6 (range 2–7). Thirty-two patients were assessable for toxicity and response. Grade 3 hematological toxicity occurred in 9% of patients and was primarily neutropenia. No grade >2 gastrointestinal toxicities or death due to treatment were observed. The most frequent nonhematological adverse event was fatigue. Ten patients responded to treatment with two complete responses (6.3%) and eight partial responses (25.0%), for an overall response rate of 31.3%; 11 patients achieved stable disease (34.3%). The median time to tumor progression and the median survival were 9.2 (95% CI: 6.0–12.4) and 11.8 (95% CI: 7.7–15.9) months, respectively, with a 2-year survival of 22%. On the basis of this trial, the combination of gemcitabine plus irinotecan, administered in a weekly schedule and at this dose, is well tolerated and offers encouraging activity in the treatment of advanced and/or metastatic pancreatic cancer.

Key words: Chemotherapy; Gemcitabine; Irinotecan; Pancreatic cancer

INTRODUCTION

Pancreatic cancer is one of the most lethal forms of cancer. It has a mortality rate of 65% within 6 months of diagnosis, which increases to more than 90% 1 year after diagnosis (1,2). Pancreatic cancer accounted for nearly 3% of all cancer reported in Europe (3). The nonspecific nature of early symptoms of this disease often results in delayed diagnosis and, consequently, 80% or more of patients initially present with uncontrollable, locally advanced, or metastatic disease. Consequently, median survival from the time of diagnosis ranges from 3 to 9 months for patients with unresectable disease (4).

Treatment options for advanced or metastatic pancreatic cancer are limited. Single-agent fluorouracil (FU) produces tumor response rates of 7% or less; combination chemotherapy with FU, anthracyclines, mitomycin-C, or cisplatin has resulted in increased toxicity without higher efficacy (5,6). Since 1997, gemcitabine (GEM), a nucleoside analog that has multiple mechanisms of action (7), has been the most widely used chemotherapeutic agent in pancreatic cancer. On the basis of preclinical studies, GEM represents an attractive candidate for combination chemotherapy of solid tumor because of its excellent side effect profile and the absence of overlapping toxicities with other antiblastic agents. Moreover, due to its chain termination masking activity, GEM directly inhibits DNA repair (8).

Irinotecan (CPT-11) has also demonstrated activity in pancreatic cancer and has a mechanism of action differ-

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ent from that of GEM. CPT-11 and its metabolites bind to topoisomerase I, inducing double-stranded DNA breaks and consequent tumor cell death (9). Thus, the combined administration of GEM and CPT-11 could result in the induction of DNA massive breaks, which are not easily repaired by the cell's machinery, thereby enhancing the apoptotic signals triggered by these lesions. Preclinical data evaluating the combination of GEM and CPT-11 suggest dose-dependent synergistic interactions in cancer cell lines (10) with no overlapping toxicities, so that their combination should be feasible.

In addition, the result of several preclinical studies (11,12) support the potential clinical value of an GEM/CPT-11 combination in pancreatic cancer. This combination has been evaluated in other two clinical studies using a dose schedule with GEM (1000 mg/m^2) and CPT-11 (100 mg/m^2) on days 1–8 of a 21-day cycle and GEM (1000 mg/m^2 on day 1–8) and CPT-11 (300 mg/m^2 on day 8) in cycles of 3 weeks (13,14). The aim of this study was to assess if the treatment schedule with the combination of GEM plus CPT-11 administered weekly can offer high response rates while providing a more favorable therapeutic index. We performed a phase II trial in order to evaluate the efficacy and tolerability of this schedule in previously untreated patients with locally advanced and/or metastatic pancreatic cancer.

PATIENTS AND METHODS

Patient Selection and Eligibility Criteria

This was a phase II study in patients with histologically confirmed advanced pancreatic carcinoma. Patients with locally advanced or metastatic pancreatic adenocarcinoma, and with evidence of measureable disease, were eligible. Additional inclusion criteria were: 75 years old or younger; informed consent; performance status (ECOG) ≤2; absence of brain metastases; absence of active infection process; absence of concomitant second primary cancer; normal cardiac, hepatic, renal, and bone marrow function; no prior chemotherapy with cytotoxic drugs. Laboratory acceptance parameters included: white blood cell count above 4000 cells/μl, a hemoglobin level not lower than 9.5 g/dl; platelet count not less than 100,000/μl; serum transaminase <3 times the upper normal limit (UNL); and bilirubin and creatinine values of <1.5 × UNL.

The study was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice and with the patient's informed written consent.

Study Design and Treatment

All the enrolled patients received chemotherapy in a day-hospital setting, with a GEM dose of 1000 mg/m^2 (IV over 30 min) and a CPT-11 dose of 100 mg/m^2 (IV over 60 min). The two agents were administered in sequence on day 1, 8, and 15 of a 28-day cycle. All patients received an antiemetic premedication with ondansetron 4 mg and metilprednisolone 8 mg, IV. Granulocyte colony stimulating growth factors (G-CSF) were not used prophylactically, while supportive care like blood transfusions or eritropoietin administration and analgesics were administered as appropriate. The planned overall duration of chemotherapy treatment was 6–8 months; however, the therapy was stopped in case of disease progression, unacceptable toxicity, or patient refusal.

Toxicity-Related Dose Reduction

Toxicity was assessed before each treatment cycle according to the WHO criteria (15). As a result, any dose reduction was calculated based on hemochrome level, liver, renal, cardiac, and pulmonary function tests. Full doses of the anticancer drugs were given if granulocyte count was >2000 μl and platelet count was >100,000 μl. In the case of grade 2 or more toxicity except alopecia, chemotherapy was discontinued for a week and than restarted after full recovery. During the study, leukocyte-stimulating growth factors were allowed in patients showing grade 3 or more neutropenia. Reduction of 25% in all the drugs dose was performed in the event of a second consecutive occurrence of grade >2 toxicity. Patients with unsolved grade 2 or more toxicity after two consecutive treatment delays or experiencing grade 3–4 nonhematological toxicity, with the exception of alopecia, went off study.

Response Evaluation

Baseline evaluation prior to treatment start included complete past medical history, through physical examination, ECG, standard chest-X-ray, and/or, when appropriate, CT scan of the chest, a complete abdominal CT scan, "total body" bone scan. At the same time, complete blood counts and renal and liver function tests were performed. These tests were repeated before any subsequent cycle. Target lesions were reevaluated after the first 3 months and at the end of treatment, through ultrasound evaluation and/or CT scan, whereas the bone scan, when appropriate, was performed only after completion of the planned cycles. According to protocol provisions, also patients who had received at least three applications of the planned treatment (one cycle) were considered evaluable for toxicity, response, and survival. Patients who withdrew from treatment before reevaluation were considered nonrespondents. Response evaluation was performed according to WHO (15) criteria. After treatment completion all patients underwent a periodical check-up every 3 months until disease progression or death.

Table 1. Patient Characteristics

Characteristics	No. of Patients (%)
Number of patients	33 (100)
Median age (years; range 41–75)	63
Gender	
Female	12 (36)
Male	21 (64)
Performance status ECOG	
0	11 (33)
1	20 (61)
2	2 (6)
Disease at presentation	
Locally advanced	22 (67)
Locally advanced and metastatic	11 (33)
No. of sites of disease	
1	10 (40)
2	17 (52)
3	6 (18)

Statistical Methods

The study was a nonrandomized, phase II study. The primary end point included objective response, toxicity, survival, and time to disease progression (TTP).

The sample size was calculated on the assumption that a percentage of objective response variable between 20% and 40% could be detected. According to the optional Simon two-step design, if a minimum objective response rate >20% was observed in the first 15 patients, an additional 15 patients should be enrolled, and if >12 responses were observed in 30 patients (40%), the regimen was considered active to be submitted for further evaluation (16). Descriptive statistics were reported as proportions and medians. Time to disease progression (TTP) was defined as the interval between initial treatment and the time of disease progression or death. Survival time was calculated from the date of treatment initiation until the date of the last follow-up evaluation or death. TTP and overall survival (OS) were analyzed according to the Kaplan-Meier method (17). The confidence intervals (CIs) for response rates, TTP, and OS were calculated using methods for exact binominal confidence interval (18). Survivors were censored on the date they were last known to be alive.

Table 2. Toxicity Type and Grade (Total Number of Treatment Cycles 188)

Toxicity	Grade 1–2 [No. (%)]	Grade 3–4 [No. (5)]
Hematologic		
Anemia	183 (97)	5 (3)
Neutropenia	174 (92)	14 (8)
Thrombocytopenia	178 (94)	10 (6)
Nonhematologic		
Alopecia	188 (100)	—
Asthenia	186 (99)	2 (1)
Diarrhoea	185 (90)	3 (2)
Mucositis	176 (98)	2 (1)
Nausea/vomiting	188 (100)	—
Cardiac	188 (100)	—
Neurologic	188 (100)	—
Pulmonary	188 (100)	—

Table 3. Response and Survival ($N = 32$ Patients)

Response	No. (%)	
Complete responses (CR)	2 (6.3)	
Partial responses (PR)	8 (25.0)	
Stable disease (SD)	11 (34.3)	
Disease progression (PD)	11 (34.3)	
Overall response (OR)	10 (31.3)	
Time (Months)	Median	95% CI
Progression time (TTP)	9.2	6.0–12.4
Overall survival (OS)	11.8	7.7–15.9

RESULTS

Patient Characteristics

Between February 2005 and April 2006, there were 33 patients with locally advanced and/or metastatic pancreatic cancer enrolled in the study. One patient could not be evaluated for response because he refused to continue treatment after the second cycle and was lost at follow-up. Final data analysis was performed in December 2007. Patient clinical characteristics are reported in Table 1. All patients had ECOG performance status ≤2 at study entry. Eleven out of 33 patients (33%) had metastases, while the remaining 22 patients (67%) had locally advanced disease. Study treatment (GEM/CPT-11) was administered as first-line therapy to all patients.

Treatment

A total of 188 treatment cycles were administered, with a median number of 5.6 cycles per patient (minimum 2 and maximum 7). Treatment was discontinued in one patient who refused to continue the cure after the second cycle (3%), in five patients (15%) due to disease progression, and in one patient (3%) due to hematological toxicity during the fifth cycle. A significant hematological toxicity was observed in this study that required G-CSF for 13 patients. In two other patients a dose reduction of 25% was necessary for both drugs (GEM/CPT-11) in seve cycles, amounting to 3.7% of the total

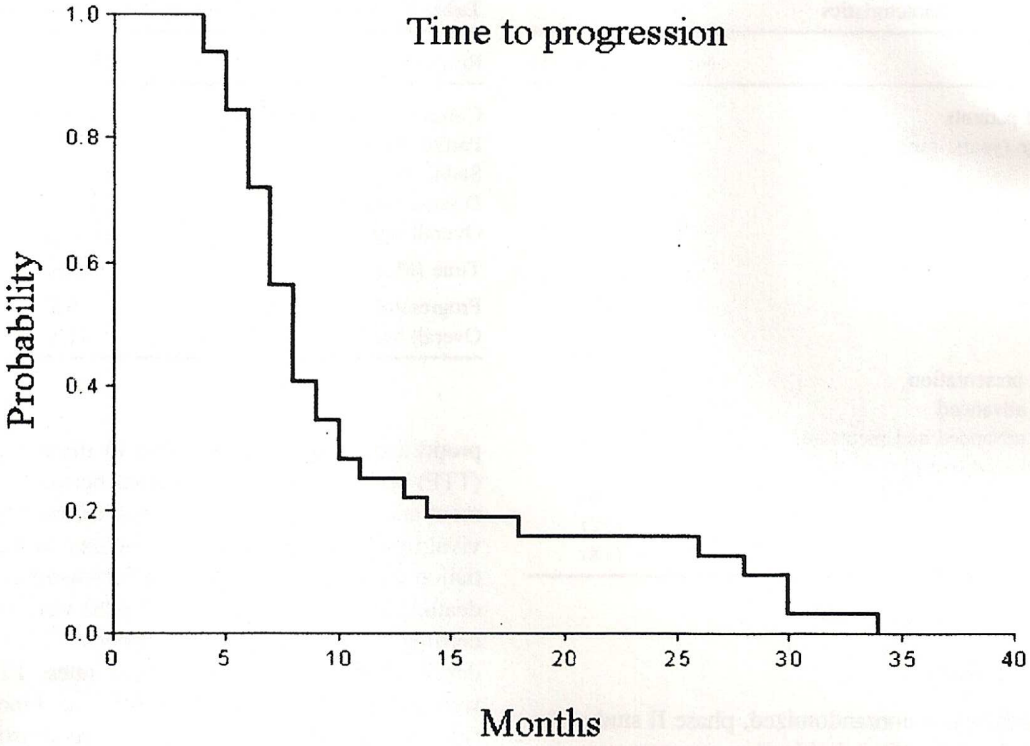

Figure 1. Kaplan-Meier estimates of time to progression among pancreatic cancer patients treated with GEM/CPT-11 weekly regimen.

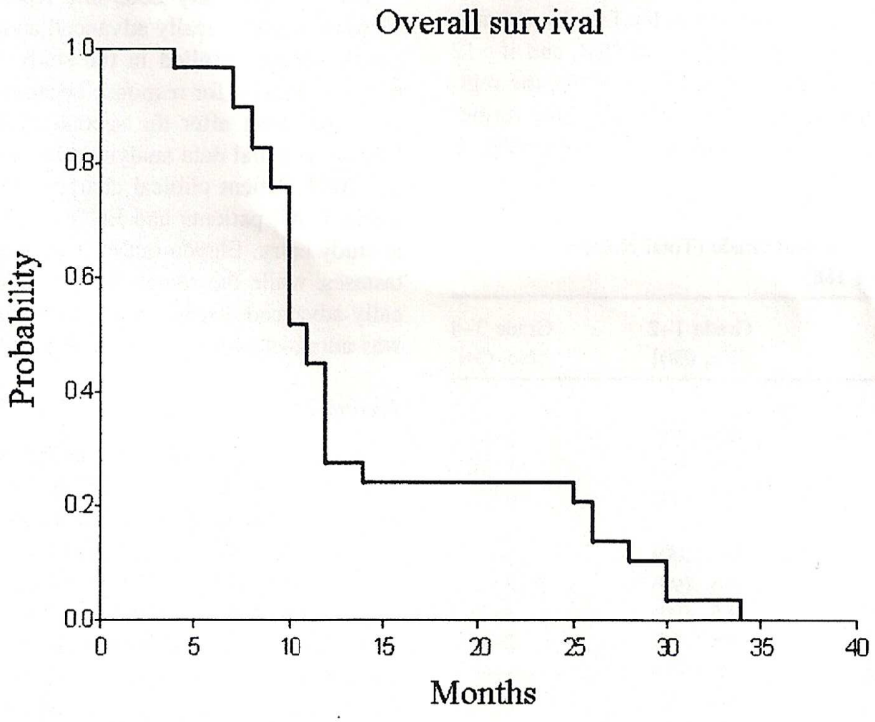

Figure 2. Kaplan-Meier estimates of overall survival among pancreatic cancer patients treated with GEM/CPT-11 weekly regimen.

number of administered cycles. Thus, at the end of study, the dose intensity actually administered was 92% of that planned.

Toxicity

All 33 patients were evaluable for toxicity. Toxicity was primarily hematologic with neutropenia being the most prominent with 14 occurrences of grade 3 and 2 episodes of febrile neutropenia, one of which required hospitalization. Less significant and frequent were anemia and thrombocytopenia. No chemotherapy-related deaths occurred, nor episodes of cardiac toxicity or changes in the lung and renal function. Among nonhematological toxicities, the most frequent was diarrhea, two episodes of grade 3 asthenia, and alopecia, which were reversible after the end of treatment. Overall toxicity, with details on type and grade, are listed in Table 2.

Treatment Response

Of the 33 patients enrolled in the study, 32 were evaluable for response, TTP, and survival. Response results are reported in Table 3. Two patients achieved a complete response (CR = 6.3%), liver and lymph nodal localization. Eight patients achieved a partial response (PR = 25.0%), giving an overall response of 31.3% (CR + PR). In addition, 11 patients achieved disease stabilization (SD = 34.3%), while the remaining 13 patients had rapid progression (PD = 40.1%). Responses are referred to measurable lesions. Skeletal lesions were not included in the response assessment because all of them were treated with pamidronate and/or radiotherapy.

After a follow-up of 31 months (range 4–31+), 25 patients died (78.1%), while the other 7 patients (21.8%) were still alive. Figures 1 and 2 report the curves of median time to progression (TTP) that was 9.2 months (range 4–31+; 95% CI: 6.0–12.4) and the median survival time that was 11.8 months (range 4–31+; 95% CI: 7.7–15.9).

CONCLUSIONS

Pancreatic carcinoma is generally considered resistant to cytotoxic therapy. Since 1997, GEM has been the most widely used chemotherapeutic agent in advanced pancreatic cancer and it achieves significantly better symptom control in this disease. However, despite these improvements, GEM monotherapy has obvious limitations in advanced and/or metastatic pancreatic cancer, and various combinations with other agents have been investigated. To date, published data concerning the combination of GEM and CPT-11 in patients with pancreatic cancer is sparse. In clinical practice, these two agents were administered in pretreated patients with pancreatic carcinoma and often combined with leucovorin, 5-fluorouracil, and cisplatin. Recent clinical studies have reported promising clinical activity with the GEM/CPT-11 combination (19–21). In this multicenter phase II study, we therefore decided to combine GEM and CPT-11 with a different schedule. In the trial, patients received a weekly administration of GEM plus CPT-11 once weekly for 3 consecutive weeks in an attempt to exploit the synergic action of the two drugs while minimizing the overall toxicity. The results of recent studies using, in advanced pancreatic cancer, different GEM/CPT-11-based regimens are reported in Table 4.

The results of the present study seem to indicate that the efficacy of the GEM/CPT-11 weekly regimen is better even when compared with other treatment schedules. This promising result, although from a small number of patients, suggests that the weekly combination therapy of GEM/CPT-11 is an active regimen in advanced or metastatic pancreatic cancer that has the advantage of being well tolerated and easily administered in an outpa-

Table 4. Results of GEM and CPT-11-Based Regimens in Advanced/Metastatic Pancreatic Cancer

Year/Study	No. Patients	Regimen	Overall Response Rate	Median TTP (Months)	Median OS (Months)
2001: Kozuch et al. (19	34	GEM/CPT-11; LV/5FU/G-FLIP (1-2 ▶ 15)	CR + PR = 24%, SD = 22%	3.9	4.7
2002: Caio Max et al. (13)	45	GEM/CPT-11 (1-8 ▶ 21)	CR + PR = 24%, SD = 35%	2.8	5.7
2003: Sthathpoulos et al. (14)	60	GEM/CPT-11 (1-8 ▶ 21)	CR + PR = 25%, SD = 37%	7.0	7.0
2004: Rocha Lima et al. (20)	169	GEM (weekly	CR + PR = 4.4%	3.0	6.6
	173	GEM/CPT-11 (1-8 ▶ 21)	CR + PR = 16%	3.5	6.3
2008: Endlicher et al. (21)	30	GEM/CPT-11; 5-FU (1-8 ▶ 21)	CR +PR = 7.1%, SD = 35	3.4	8.3
2008: This study	33	GEM/CPT-11 (1-8-15 ▶ 28)	CR + PR = 31.3%, SD = 31.3%	9.2	11.8

tient setting. In conclusion, the efficacy of this regimen (high response rate and long median survival duration), coupled with the acceptable toxicity observed, indicate that this combination is an interesting candidate for future comparisons with other GEM-based regimens. Moreover, our future efforts will focus on randomized trials evaluating this GEM/CPT-11 schedule in patients with earlier stage disease as adjuvant chemotherapy.

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