Gemcitabine Alone or with Cisplatin for the Treatment of Patients with Locally Advanced and/or Metastatic Pancreatic Carcinoma

A Prospective, Randomized Phase III Study of the Gruppo Oncologico dell'Italia Meridionale

Giuseppe Colucci, M.D.[1]
Francesco Giuliani, M.D.[1]
Vittorio Gebbia, M.D., Ph.D.[2]
Maria Biglietto, M.D.[3]
Piergiorgio Rabitti, M.D.[4]
Generoso Uomo, M.D.[5]
Silvio Cigolari, M.D.[6]
Antonio Testa, M.D.[2]
Evaristo Maiello, M.D.[1]
Massimo Lopez, M.D.[7]

[1] Medical and Experimental Oncology Unit, Oncology Institute, Bari, Italy.

[2] Medical Oncology Unit, La Maddalena Oncological Hospital, Palermo, Italy.

[3] Division of Medical Oncology, Cardarelli Hospital, Napoli, Italy.

[4] XI Internal Medicine and Diabetology, Cardarelli Hospital, Napoli, Italy.

[5] III Internal Medicine, Cardarelli Hospital, Napoli, Italy.

[6] III Internal Medicine, University of Napoli, Napoli, Italy.

[7] Division of Medical Oncology, Oncology Institute Regina Elena, Roma, Italy.

Presented in part at a meeting of the American Society of Clinical Oncology, Atlanta, Georgia, May 15–18, 1999.

The following investigators are members of the Gruppo Oncologico dell'Italia Meridionale and are coauthors of the article: Severino Montemurro, M.D. (Oncology Institute, Bari); Fernando Riccardi, M.D. (Cardarelli Hospital, Napoli); Nicoló Gebbia, M.D., Ph.D. (University of Palermo, Palermo); Giuseppe Pezzella, M.D. (SS. Annunziata Hospital, Taranto); Salvatore Cariello, M.D. (San Giovanni di Dio e Ruggi d'Aragona Hospital, Salerno); Cesare Bumma, M.D. (San Giovanni Antica Sede, Torino); Antonio Pedicini, M.D. (Fatebenefratelli Hospital, Benevento); Giuseppina Fallica, M.D. (Oncology Center, Catania); Giancarlo Paoletti, M.D. (Oncology Institute Regina Elena, Roma).

Address for reprints: Giuseppe Colucci, M.D., Medical and Experimental Oncology Unit, Oncology Institute, Via Amendola 209, 70125 Bari, Italy; Fax: 39-080-5555483; E-mail; colucci@goim.it

Received February 28, 2001; revision received September 12, 2001; accepted October 23, 2001.

BACKGROUND. A prospective, randomized Phase III trial was performed to determine whether, compared with gemcitabine (GEM) alone, the addition of cisplatin (CDDP) to GEM was able to improve the time to disease progression and the clinical benefit rate in patients with advanced pancreatic adenocarcinoma. The objective response rate, overall survival rate, and toxicity patterns of patients in the two treatment arms were evaluated as secondary end points.

METHODS. Patients with measurable, locally advanced and/or metastatic pancreatic adenocarcinoma were randomized to receive GEM (Arm A) or a combination of GEM and CDDP (Arm B). In Arm A, a dose of 1000 mg/m^2 GEM per week was administered for 7 consecutive weeks, and, after a 2-week rest, treatment was resumed on Days 1, 8, and 15 of a 28-day cycle for 2 cycles. In Arm B, CDDP was given at a dose of 25 mg/m^2 per week 1 hour before GEM at the same dose that was used in Arm A. On Day 22, only GEM was administered. Patients were restaged after the first 7 weeks of therapy and then again after the other 2 cycles.

RESULTS. A total of 107 patients entered the trial: Fifty-four patients were randomized to Arm A, and 53 patients were randomized to Arm B. The median time to disease progression was 8 weeks in Arm A and 20 weeks in Arm B; this difference was statistically significant ($P = 0.048$). In Arm A, one complete response and four partial responses were recorded on the basis of an intent-to-treat analysis, with an overall response rate of 9.2% (95% confidence interval [95%CI], 3–20%). In Arm B, there were no complete responses, whereas 14 partial responses were achieved, with an overall response rate of 26.4% (95%CI, 15–40%). This difference in the overall response rates was statistically significant ($P = 0.02$). The tumor growth control rate (i.e., total number of patients who achieved complete responses, partial responses, and stable disease) was 42.6% (95%CI, 29–57%) in Arm A and 56.6% (95%CI, 42–70%) in Arm B. A clinical benefit was observed in 21 of 43 patients (49%) in Arm A and in 20 of 38 patients (52.6%) in Arm B without any significant difference. The median overall survival was 20 weeks for patients in Arm A and 30 weeks for patients in Arm B ($P = 0.43$). Toxicity was mild in both treatment arms, with no significant differences between the two groups except for the statistically higher incidence of Grade 1–2 asthenia in Arm B ($P = 0.046$).

CONCLUSIONS. The addition of CDDP to GEM significantly improved the median time to disease progression and the overall response rate compared with GEM alone. The clinical benefit rate was similar in both arms, whereas the median overall survival rate was more favorable for Arm B, although the difference did not attain statistical significance. The authors conclude that the combination of CDDP and GEM currently may be considered as an optimal treatment for patients with locally advanced and/or metastatic adenocarcinoma of the pancreas. ***Cancer* 2002; 94:902–10.**
DOI 10.1002/cncr.10323

KEYWORDS: pancreatic adenocarcinoma, gemcitabine, cisplatin, chemotherapy, metastases.

Carcinoma of the exocrine pancreas is a malignant neoplasm, and patients with this disease have an extremely poor prognosis and a 5-year overall survival (OS) rate $< 2\%$. At the time of diagnosis, most patients have locally advanced and/or metastatic disease and experience severe pain, nausea and emesis, anorexia, and significant weight loss, symptoms that have a substantial negative effect on the patients' performance status (PS) and quality of life. The median survival for these patients ranges from 3 months to 6 months.[1]

Chemotherapy is used widely in the treatment of patients with advanced stage pancreatic adenocarcinoma (APCa) in an attempt to improve survival and to control disease-related symptoms.[2,3] Traditionally, 5-fluorouracil (5-FU) has been considered the most effective drug for the treatment of patients with APCa. In the past 2 decades, several clinical investigations using a variety of doses and modalities for the administration of 5-FU have been performed, but the objective response (OR) rates achieved were only 0–10%.[4] 5-FU-containing polychemotherapeutic regimens have provided OR rates ranging from 15% to 40% in Phase II studies,[5–8] but none of the randomized trials that compared combination regimens with monochemotherapy have demonstrated the superiority of any multidrug treatment over 5-FU alone.[9–12]

Biochemical modulation of 5-FU by folinic acid (FA) has yielded some clinical benefits in patients with colorectal carcinoma but has failed to ameliorate clinical results in the treatment of patients with APCa. Collective data from four studies that included over 100 patients showed that this approach had low antineoplastic activity, with a 7% overall OR rate.[13–16]

It has been demonstrated that gemcitabine (2,2-difluorodeoxycytidine; GEM), a deoxycytidine analogue, is effective in a variety of solid malignant tumors. The drug acts by intracellular activation into phosphorylated metabolites, such as gemcitabine-triphosphate, which competes with endogenous deoxycitidine triphosphate for incorporation into DNA, and gemcitabine-diphosphate, which inhibits ribonucleotide reductase, the key enzyme in the formation of deoxynucleotide triphosphates necessary for normal DNA synthesis. Three biochemical mechanisms underlie the so-called self-potentiation process of GEM activity: 1) inhibition of ribonucleotide reductase; 2) stimulation of deoxycitidine kinase, the enzyme responsible for GEM activation; and 3) inhibition of deoxycitidine monophosphate deaminase, the enzyme responsible for GEM degradation.[17,18]

In the first-line treatment of two series of 35 and 32 evaluable patients with APCa, GEM was administered weekly at escalating doses from 800 mg/m^2 to 1000–1250 mg/m^2 for 3 weeks out of every 4 weeks and yielded OR rates of 6% and 11%, respectively.[19,20] In those two trials, the median OS was 5.6 months and 6.3 months, respectively. An OR rate of 16.6% was reported when GEM was administered initially at a dose of 1000 mg/m^2 once each week for 7 consecutive weeks and thereafter for 3 weeks out of every 4 weeks.[21] In all of these Phase II trials, some patients experienced a significant improvement in disease-related symptoms.

In a large, randomized Phase III trial, single-agent GEM was compared with 5-FU alone[22]: patients who were included in the GEM arm showed a statistically longer median OS (5.65 months vs. 4.42 months; $P = 0.0025$) and a significant improvement in the clinical benefit (CB) rate (23.8% vs. 4.8%; $P = 0.0022$) compared with patients who were treated with 5-FU, respectively. The CB rate was defined on the basis of improvement in two primary clinical parameters, i.e., PS and pain, and one secondary parameter, weight loss. The OR rate was 5.4% in the GEM arm, whereas no objective response was observed in the 5-FU arm. On the basis of these data, GEM has been considered the drug of choice for the treatment of patients with APCa and is administered mainly to ameliorate tumor-related symptoms and quality of life.

Many attempts have been made to increase the overall OR rate and survival of patients with APCa, in particular, by exploring the combination of GEM with other drugs. It has been shown that cisplatin (CDDP) has a 21% overall OR rate with a median OS of only 4 months among patients with APCa.[23] Although the activity of CDDP alone may be overestimated, it has been shown that the combination of GEM and CDDP is synergistic in vitro, because GEM is able to inhibit DNA repair after CDDP-induced damage, and CDDP is able to influence GEM catabolism through the inhibition of ribonucleotide reductase.[24,25] Many trials have demonstrated the efficacy of this combination in the treatment of patients with various malignancies, such as nonsmall cell lung carcinoma[26,27] and bladder carcinoma.[28,29] In a Phase II study, doses of 1000 mg/m^2 GEM on Days 1, 8, and 15 of a 28-day cycle plus 50 mg/m^2 CDDP on Days 1 and 15 produced 1 complete response and 3 partial responses in 35 evaluable patients with APCa, for an overall response rate of 11.5% and a median OS of 8.3 months.[30] In another study of 22 evaluable patients with APCa, this combination regimen yielded 2 complete responses and 6 partial responses, for an overall response rate of 36.6% and a median OS of 7.4 months.[31]

Based on these results, the Gruppo Oncologico dell'Italia Meridionale (GOIM) carried out a multicenter, prospective, randomized Phase III trial comparing the combination of CDDP plus GEM with GEM alone in the treatment of patients with advanced and/or metastatic pancreatic carcinomas. The primary objective of the study was to establish whether

treatment with CDDP plus GEM was superior to single-agent GEM in terms of the time to progression (TTP) and the CB rate, and the secondary objective was to compare the OR rates, OS rates, and patterns of toxicity of the two treatments.

MATERIALS AND METHODS

Patient Selection and Study Design

After approval by the GOIM Scientific Committee, patients were enrolled into the study if they met the following inclusion criteria: 1) histologic or cytologic diagnosis of locally advanced and/or metastatic pancreatic carcinoma; 2) bidimensionally measurable disease according to standard World Health Organization (WHO) criteria, 3) no previous chemotherapy, hormonal therapy, or radiotherapy; 4) age 18–75 years; 5) PS $\geq$ 50 according to the Karnofsky index; 6) no evidence of congestive heart failure, serious arrhythmias, or coronary artery disease; 7) absence of severe uncontrolled metabolic, infectious, or neurologic disease; and 8) absence of other malignant neoplasms with the exception of adequately treated in situ carcinoma of the uterine cervix or nonmelanotic skin carcinoma. Informed, written consent also was requested from all patients before their inclusion into the study.

Other requirements included adequate baseline bone marrow reserve (white blood cell count $\geq$ 4000/mm^3, neutrophils $\geq$ 1500/mm^3, platelets $\geq$ 100,000/mm^3, and hemoglobin level $\geq$ 10g/dL), adequate hepatic function (levels of bilirubin and transaminases $\leq$ 2.5 times normal values), and adequate renal function (defined as serum creatinine concentration $\leq$ 1.5 mg/dL and blood urea nitrogen $\leq$ 50 mg/dL). Patients were excluded from the trial in the presence of brain metastases or any preexisting medical condition of sufficient severity to prevent full compliance with the study. Geographic accessibility also was considered a prerequisite to guarantee correct therapy and follow-up.

Sample size was calculated considering a mean 4-month progression free rate of 25–30% after treatment with GEM alone, as indicated elsewhere in the medical literature. Hence, each treatment arm had to enroll 53 patients to demonstrate a 30% improvement in TTP with the experimental treatment at the significance level of α error 0.05% with a power of β 0.8.

Treatment Schedule

Patients were registered centrally at the GOIM headquarters at the Oncology Institute of Bari, Italy, and were randomized to receive GEM alone (Arm A) or GEM plus CDDP (Arm B). In Arm A, GEM was administered as a 30-minute intravenous infusion once per week for 7 consecutive weeks at a dose of 1000 mg/m^2 weekly diluted in 250 mL of normal saline solution; after a 2-week rest, the same treatment was continued on Days 1, 8, and 15 of a 28-day cycle for 2 cycles. In Arm B, on Days 1, 8, 15, 29, 36, and 42 of a 7-week cycle, 1 hour infusion of CDDP was administered at a dose of 25 mg/m^2 weekly diluted in 500 mL of normal saline to ensure adequate hydration 1 hour before the administration of GEM at the same dose that was used in Arm A; on Day 22, only GEM was administered; after a 2-week rest, treatment was continued on Days 1, 8, and 15 of a 28-day cycle for 2 cycles (Fig. 1). Antiemetic therapy consisted of anti-HT3 agent and dexametasone. Granulocyte-colony stimulating factor was not administered routinely in this study.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria. If multiple toxicities were observed, then the dose administered was based on the most severe toxicity experienced. The dose-adjustment schedule was evaluated at the beginning of a new administration and was based on the following criteria: If the absolute neutrophil count (ANC) was $\geq$ 1000/mm^3 and platelets were $\geq$ 100,000/mm^3, then 100% of the dose was administered. If the ANC was in the range of 500–1000/mm^3 and platelets were in the range of 50,000–100,000/mm^3, then 75% of the dose was administered. If the ANC was $<$ 500/mm^3 and platelets were $<$ 50,000/mm^3, then treatment was delayed for 1 week.

Pretreatment Evaluation and Follow-Up

Staging procedures consisted of a complete medical history and physical examination; electrocardiogram;, complete peripheral blood cell counts; and serum chemistry panel, including serum tumor markers (carcinoembryonic antigen and Ca19-9). Bidimensionally measurable disease was determined by chest X-rays, ultrasonography and/or computed tomographic scanning, and/or nuclear magnetic resonance imaging, as needed. Elevated carcinoembryonic antigen levels were not considered measurable disease. Endoscopy was employed according to patients' needs. After withdrawal from the study, patients underwent follow-up examinations every 2 months until death.

Efficacy Assessment

The first evaluation of disease status and CB was performed after the first cycle (seven weekly administrations). Patients who achieved a complete response (CR) or a partial response (PR) and patients with stable disease (SD) continued treatment and were reevaluated after 2 28-day cycles. Objective responses (ORs) were determined according to WHO criteria: a CR was defined as the complete disappearance of all disease sites and of all disease-related symptoms with no evidence of new lesions for at least 4 consecutive weeks; a PR was defined as a reduction $\geq$ 50% in the sum of the products of all measurable lesions without any

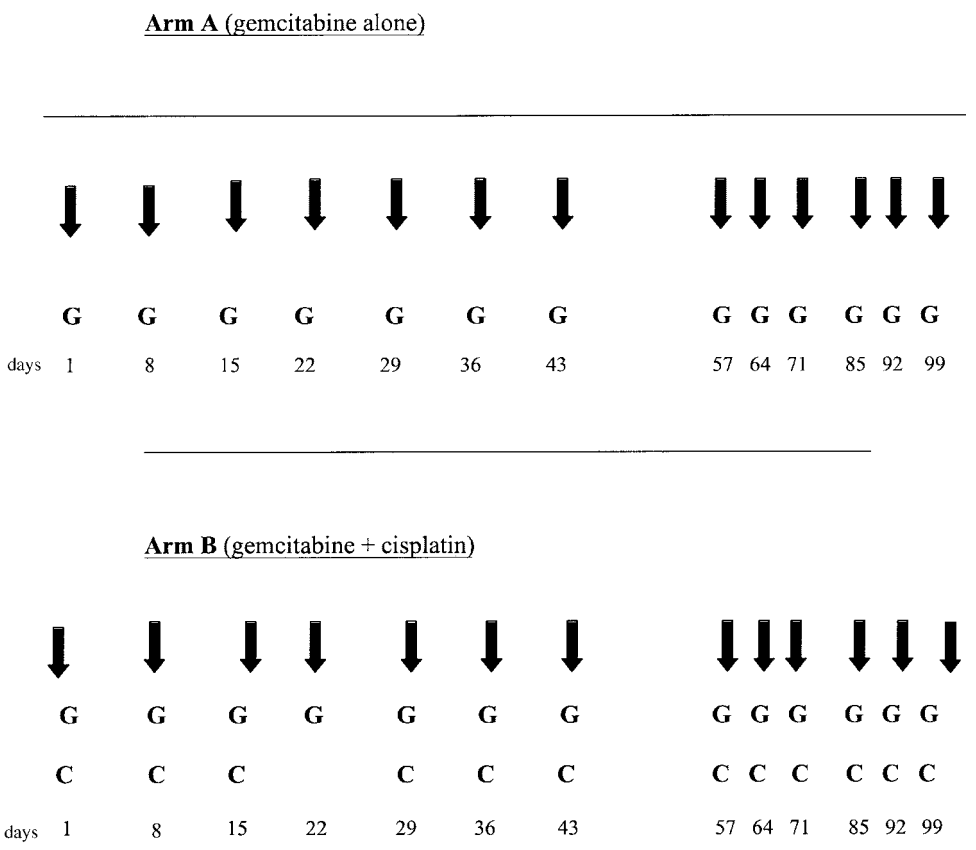

FIGURE 1. Treatment schedules. G: gemcitabine 1000 mg/m^2 by 30-minute, intravenous infusion; C: cisplatin 25 mg/m^2 by intravenous infusion.

evidence of new lesions; SD was defined as a reduction $< 50\%$ or an increase $< 25\%$ in the sum of the products of the measurable lesions with no evidence of new lesions; and progressive disease (PD) was defined as an increase $\geq 25\%$ in 1 or more lesions or the appearance of new lesions. The time to tumor progression was estimated from the date of the first treatment to the first evidence of disease progression. Survival was estimated from the date of the first treatment to the date of death or last follow-up. Response rates were provided for evaluable patients and for all patients according to an intent-to-treat (ITT) analysis.

The CB assessment was based on the measurement of three common signs or symptoms, two of which (pain and functional impairment) were defined as primary, and one of which (weight loss) was defined as secondary. Pain was assessed by pain intensity and analgesic consumption. Pain intensity was determined daily by a visual analogic scale, and the weekly value was defined as the median of all recorded daily values; an improvement $> 50\%$ from baseline that was sustained for ≥ 4 weeks was considered a positive response, assuming a baseline pain score of 30. Analgesic consumption was recorded weekly employing the following scale: 0, no analgesic consumption; 1, administration of nonsteroidal anti-inflammatory drugs; 2, consumption of codeine phosphate; 3, oral administration of morphine sulfate; 4, parenteral administration of morphine; and 5, neurosurgical procedures. A change from a higher level to a lower level was considered a positive response. When consumption of analgesic drugs was considered within each level, patients who required an increase in their daily dose were defined as nonresponders.

Functional impairment was assessed by the Karnofsky performance scale (PS). Baseline values were determined weekly by two different investigators. For patients with a PS of 50, 60, or 70, an improvement of > 20 points from baseline that was sustained for > 4 weeks was considered a positive response. Weight was measured weekly, and a weight gain $> 7\%$ (excluding third spaces) that was sustained for > 4 weeks was considered a positive response. Therefore, a patient was classified as a CB responder if one of the two primary parameters improved without deterioration in the others or if the primary parameters were stable and a weight gain $> 7\%$ from baseline was observed.

Statistical Analysis

Objective responses were reported according to an ITT analysis of evaluable patients. The balance of clin-

TABLE 1
Patient Characteristics

Characteristic	GEM (%)	CDDP and GEM (%)
Enrolled patients.	54 (100)	53 (100)
Gender		
Male	27 (50)	35 (66)
Female	27 (50)	18 (34)
Age (yr)		
Median	63	60
Range	43–75	33–71
Karnofsky PS		
Median	70	70
Range	50–100	50–100
Stage		
II	11 (20)	10 (19)
III	14 (26)	10 (19)
IV	29 (54)	33 (62)
Surgery		
Radical	4 (7)	7 (13)
Biopsy	50 (93)	46 (87)
Sites of disease		
Pancreas	50 (92)	46 (87)
Liver	23 (42)	26 (49)
Lymph nodes	21 (39)	20 (38)
Lung	3 (5)	2 (4)
Other	5 (9)	3 (6)
Sites		
Single	19 (35)	17 (32)
Multiple	35 (65)	36 (68)

GEM: gemcitabine; CDDP: cisplatin; PS: performance status.

ical characteristics between the two groups as well as differences in OR rates were analyzed applying a chi-square test for Fisher analysis to a contingency table. The univariate Kaplan–Meier product-limit analysis was computer generated and employed to evaluate TTP and OS. Statistical analysis was performed by the log-rank test to compare differences in survival data distribution between the two groups.

RESULTS

Patient Population and Disease Status

A total of 107 patients entered the trial; 54 patients were randomized to Arm A, and 53 patients were randomized to Arm B. The main demographic and clinical characteristics of the enrolled patients are summarized in Table 1.

Overall, 62 patients were male (58%), and 45 patients were female (42%), with a median age of 62 years (range, 33–75 years) and a median Karnofsky PS of 70 (range, 50–100). Few patients (10.2%) had recurrent disease after radical surgery, whereas most patients had locally advanced and/or metastatic disease. Seventy-six percent of patients had multiple sites of disease that included mainly the primary pancreatic tumor, lymph node disease, and liver metastases in both groups. The two treatment arms were well balanced in terms of age distribution, PS, disease stage, sites of disease, and number of sites.

TABLE 2
Objective Response Rate, Time to Disease Progression, and Overall Survival

Variable	GEM (%)	CDDP and GEM (%)	*P* value
Objective response			
Enrolled patients	54 (100)	53 (100)	—
Evaluable patients	48 (89)	45 (85)	—
CR	1 (1.8)	—	—
PR	4 (7.4)	14 (26.4)	—
SD	18 (33.3)	16 (30.2)	—
PD	25 (46.3)	15 (28.3)	—
Objective response rate			
Evaluable patient:	10.4	31.1%	0.01
ITT analysis	9.2	26.4	0.02
TTP and OS analysis			
Median time to progression (weeks)	8	20	0.048
Median overall survival (weeks)	20	30	0.48

GEM: gemcitabine; CDDP: cisplatin; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ITT: intent to treat; TTP: time to progression; OS: overall survival.

The main disease sites were the primary tumor (92% of patients in Arm A vs. 87% of patients in Arm B), the liver (42% of patients in Arm A vs. 49% of patients in Arm B), and the lymph nodes (38% of patients in both groups). Twenty-seven patients in Arm A (50%) and 31 patients in Arm B (57%) had metastatic disease, whereas 27 patients in Arm A (50%) and 21 in Arm B (40%) had locally advanced tumors; multiple disease sites were observed in 35 patients in Arm A (65%) and in 36 patients in Arm B (68%).

Objective Response, TTP, and OS

In Arm A, 48 of 54 enrolled patients (89%) were available for objective response evaluation, 3 patients were not evaluable for response due to toxicity unrelated withdrawal from treatment before re-evaluation, and 3 patients were not evaluable because of protocol violation for incomplete reassessment or consumption of alternative drugs. In Arm B, 45 of 53 enrolled patients (84%) were available for objective response, and 8 patients were not assessable for the following reasons: 1 refusal because of treatment-related side effects, 2 refusals unrelated to toxicity, and 5 protocol violations because of patient self-administration of alternative therapies.[32]

OR rates, CB rates, median TTP, and OS rates are depicted in Table 2. There was a mean of 1.79 cycles (8.85 administrations) in Arm A and 2.2 cycles (10.4 administrations) in Arm B. According to an ITT analysis, 1 CR (1.8%) and 4 PRs (7.4%) were observed in

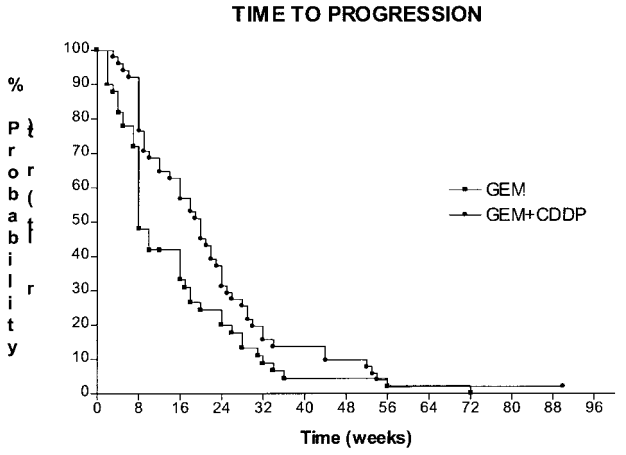

FIGURE 2. Time to disease progression in the two treatment arms. GEM: gemcitabine; CDDP: cisplatin.

Arm A with a 9.2% OS rate (95% confidence interval [95%CI], 3.0–20%), 18 patients (33.3%) had SD with a tumor growth control rate (objective responses plus SD) of 42.6% (95%CI, 29–57%), and 25 patients (46.3%) showed PD. In Arm B, 14 PRs were observed with a 26.4% OR rate (95%CI, 15–40%), 16 patients (30.2%) had SD with a tumor growth control rate of 56.6% (95%CI, 42–70%), and 15 patients (28.3%) had PD. The difference in the OR rates of the two treatment arms was statistically significant ($P = 0.02$). In the evaluable patients, the OR rate was 10.4% in Arm A compared with 31.1 in Arm B. ($P = 0.01$).

The median objective response duration was 28 weeks in Arm A (range, 20–72 weeks) and 31 weeks in Arm B (range, 26–90 weeks), and the median duration of SD was 18.0 weeks and 19.5 weeks, respectively. The response rate according to disease site was as follows: for Arm A, primary tumor in 11% of patients, liver in 10% of patients, and lymph nodes in 6% of patients; for arm B, primary tumor in 29% of patients, liver in 23% of patients, and lymph nodes in 24% of patients.

The median TTP was 8 weeks for Arm A and 20 weeks for arm B; as shown in Figure 2, this difference was statistically significant ($P = 0.048$; hazard ratio, 1.49). Statistical ITT analysis of the median OS showed a more favorable trend for Arm B, with an OS rate of 20 weeks in Arm A and 30 weeks in Arm B: however, this difference did not attain statistical significance ($P = 0.48$; Table 2). In Arm A, responders had a median survival of 46 weeks compared with 20 weeks for nonresponders ($P = 0.08$). In arm B, the median survival of responders was 39 weeks compared with 20 weeks for nonresponders ($P = 0.01$). Seventeen patients were alive at 6 months (31.5%), and 6 patients (11%) were alive at 12 months in Arm A; whereas 25 patients (47%) were alive at 6 months, and 6 patients (11.3%) were alive at 12 months in Arm B.

TABLE 3
Results of the Clinical Benefit Analysis

Variable	GEM (%)	CDDP and GEM (%)	*P* value
Evaluable for clinical benefit	43	38	—
Pain and performance	32 (74)	19 (50)	—
Only pain	9 (21)	16 (42)	—
Only performance	2 (5)	3 (8)	—
Responders	21 (49)	20 (53)	NS
Pain	9	16	—
Pain and performance	11	3	—
Weight	1	1	—

GEN: gemcitabine; CDDP: cisplatin; NS: not significant.

CB

Forty-three of 54 patients (80%) enrolled in Arm A (GEM) and 38 of 53 patients (72%) enrolled in Arm B (GEM plus CDDP) were evaluable for CB assessment, as shown in Table 3. In the GEM arm, 32 patients (74%) were evaluable for both primary parameters (i.e., pain and PS), 9 patients (21%) were evaluable only for pain, and 2 patients (5%) were evaluable only for PS. In the combination arm, 19 patients (50%) were evaluable for both pain and PS, 16 patients (42%) were evaluable only for pain, and 3 patients (8%) were evaluable only for PS. Both pain and PS improved in 11 patients who were treated with GEM alone, and 9 additional patients demonstrated an improvement in pain without deterioration of PS; another patient showed a weight increase $> 7\%$ with no change in pain or PS. Hence, 21 patients (49%) were classified globally as CB responders in Arm A. In the combination arm, both pain and PS improved in 3 patients, whereas 16 patients showed a decrease in pain without deterioration of PS, and 1 patient showed a weight increase $> 7\%$ with no change in pain and PS. Thus, 20 patients (52.6%) were classified globally as CB responders in Arm B. Improvement in the CB parameters was observed in both treatment groups after the fourth week of administration.

Toxicity

In total, 53 patients in Arm A and 51 patients in Arm B were evaluable for toxicity. Three patients (one patient in Arm A and two patients in Arm B) were not assessable because of protocol violation consisting of the consumption of alternative antineoplastic drugs since the first administration of chemotherapy. The main toxicities recorded are listed in Table 4.

The two treatments generally were tolerated very well by most patients, and no treatment-related deaths were observed. Overall, the most frequent toxicities were represented by gastrointestinal and hema-

TABLE 4
Toxicity Recorded According to the National Cancer Institute Common Toxicity Criteria

	GEM (%) (n = 53 patients)		CDDP and GEM (%) (n = 51 patients)	
Toxicity	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Mucositis	2 (4)	1 (2)	3 (6)	—
Diarrhea	5 (9)	—	5 (10)	2 (4)
Nausea/emesis	27 (51)	1 (2)	33 (65)	1 (2)
Leukopenia	25 (47)	2 (4)	30 (59)	2 (4)
Neutrophils	4 (7)	5 (9)	6 (12)	9 (18)
Anemia	12 (23)	2 (4)	14 (27)	3 (6)
Platelets	15 (28)	1 (2)	16 (31)	1 (2)
Transaminases	8 (15)	1 (2)	7 (14)	—
Fever	5 (9)	—	5 (10)	—
Alopecia	1 (2)	—	6 (12)	—
Flu-like syndrome	13 (25)	—	6 (12)	—
Asthenia	5 (9)	—	12 (24)	—
Cutaneous	—	—	2 (4)	—

GEM: gemcitabine; CDDP: cisplatin.

tologic side effects and flu-like syndrome. The main differences between the two arms were noted in the incidence of Grade 1–2 nausea and emesis (Arm A, 51%; Arm B, 65%), Grade 1–2 leukopenia (Arm A, 47%; Arm B, 59%), Grade 1–2 neutropenia (Arm A, 7%; Arm B, 12%), and Grade 3–4 neutropenia (Arm A, 9%; arm B, 18%). None of these differences was statistically significant. Grade 3–4 diarrhea was absent in Arm A, whereas it had a 4% incidence rate in Arm B. Grade 1–2 asthenia was reported more frequently in Arm B than in Arm A (24% vs. 9%, respectively) together with alopecia (Arm A, 2%; Arm B, 12%). The difference in the incidence of Grade 1–2 asthenia was statistically significant ($P = 0.046$). No difference was observed between the two arms for anemia, thrombocytopenia, mucositis, and diarrhea.

DISCUSSION

To our knowledge, the current study is the first prospective, randomized Phase III trial comparing single-agent GEM with combined GEM plus CDDP in the treatment of patients with APCa. Currently, GEM is considered the standard treatment for patients with APCa by most oncologists on the basis of the results obtained in Phase II–III trials reporting a CB response in 23–40% of patients, a major OR rate ranging from 5.4% to 16.6%, disease stabilization in 19–40% of patients, and a median survival ranging from 3.9 months to 6.3 months. The Investigational New Drug Treatment Program reported a 12% OR rate, including 14 clinical CRs, in 982 patients with APCa who were treated with single-agent GEM. The survival data from 2380 patients showed that the median survival was 4.8 months, with a 1-year survival rate of 15%.[33] Compared with single-agent 5-FU, GEM alone was significantly more effective in terms of CB and OS.[22]

Recently, to improve the clinical results of single-agent GEM, some Phase II trials have evaluated the efficacy of combinations of GEM with other drugs that were shown to be synergistic in vitro, such as 5-FU and CDDP. Overall, in combination with 5-FU with or without FA, GEM seems to be active in terms of disease stabilization and OS, but it does not obtain a significant OR rate, and it is associated with a toxicity pattern, the severity of which depends in part on the 5-FU administration schedule. Hidalgo et al.[34] tested GEM 700–1000 mg/m^2 on a weekly schedule plus 5-FU 200 mg/m^2 per day administered as a protracted venous infusion and achieved a 19% OR rate, a median TTP of 7.4 months, and an OS of 10.3 months, with a significant incidence of Grade 3–4 hematologic and gastrointestinal toxicities. Cascinu et al.[35] employed 5-FU 600 mg/m^2 and GEM 1000 mg/m^2 weekly for 3 weeks out of every 4 weeks in 54 patients with APCa and obtained a 6% OR rate and a 63% SD rate, with a median OS of 7 months. Louvet et al.[36] employed GEM 1000–1500 mg/m^2 plus FA 400 mg/m^2 in a 2-hour infusion followed by a bolus of 400 mg/m^2 5-FU and 3000 mg/m^2 as a 48-hour continuous venous infusion in a series of 48 evaluable patients, achieving an objective response in 19% of the patients and CB in 50%, with a median TTP of 4.5 months and a median OS of 8 months. Grade 3–4 neutropenia was observed in 23% of cycles, Grade 3–4 thrombocytopenia and mucositis were observed in 6% of cycles, and severe diarrhea was observed in 2.5% of cycles. GEM also has been tested in combination with taxotere without any significant results, with an OR rate of about 7%. The combination of GEM with taxotere or epirubicin yielded a 7–21% OR rate but with high hematologic toxicity.[37,38]

Heinemann et al.[30] used GEM 1000 mg/m^2 per week for 3 weeks and CDDP 50 mg/m^2 on Days 1 and 15 every 4 weeks in 35 evaluable patients with APCa and achieved an OR rate of 11.5% and an SD rate of 57%; the TTP was 4.3 months, and the median OS was 8.2 months. A similar schedule was employed by Philip et al.,[31] who reported a 36.4% OR rate and a 27% SD rate in 22 evaluable patients, with a TTP of 6.2 months and a median OS of 7.4 months.

In the current study, the weekly administration of CDDP was chosen to optimize the potential synergism between CDDP and GEM. The two treatment arms were well balanced in terms of general demographic and clinical characteristics, with the exception of a slightly greater number of female patients in Arm A. The median TTP in the combination arm was twice as long as the TTP recorded in the GEM alone arm (20

weeks vs. 8 weeks). This difference was statistically significant ($P = 0.048$). According to an ITT analysis, the OR rate was 9.2% in the single-agent GEM arm and 26.4% in the GEM plus CDDP combination arm. This difference also was statistically significant ($P = 0.02$). Eighteen patients (33.3%) in Arm A (GEM alone) and 16 patients (30.2%) in Arm B (GEM plus CDDP) had SD, with a tumor growth control rate of 42.6% in Arm A and 56.7% in Arm B. The median OS in the two treatment arms also was different: 20 weeks in the single-agent GEM arm and 30 weeks in the combination arm. Despite this trend, the difference did not reach statistical significance. The two treatments showed a similar efficacy in terms of CB: twenty-one of 43 patients (49%) in Arm A and 20 of 35 patients (52.6%) in Arm B were classified as responders.

The 9.2% OR rate and the 20-week (5 months) median OS obtained with single-agent GEM in the current study are in the range reported in the medical literature and are close to the 12% OR rate and the 4.8-month OS reported in the review by Storniolo et al.[33] The activity of GEM plus CDDP in this study clearly was better compared with the activity of single-agent GEM in terms of median TTP and OR rate. The results achieved in the GEM plus CDDP arm are similar to those reported in the Phase II trials by Heinemann et al.[30] and Philip et al.[31] in terms of the tumor growth control rate (57% vs. 68% vs. 64%, respectively), median TTP (5.0 months vs. 4.3 months vs. 6.2 months, respectively), and median OS (7.5 months vs. 8.2 months vs. 7.4 months, respectively). Moreover, more than 50% of patients experienced a CB response.

The toxicity observed with the CDDP plus GEM regimen in our study seems to be lower than the toxicity reported by Heinemann et al.[30]: low percentages of Grade 3–4 leukopenia (4%), neutropenia (18%), anemia (6%), and diarrhea (4%) were reported in our study, whereas Heinemann et al. and Philip et al.[31] reported neutropenia in 35% and 46% of their patients, respectively, thrombocytopenia in 29% and 54%, anemia in 13% and 42%, and nausea and emesis in 13% and 19%. These differences in the severity of toxicity most likely are related to the different doses employed and the modality of CDDP administration.

In our study, both treatments were well tolerated globally. Although nausea and emesis, leukopenia, and neutropenia were slightly more frequent in the combination arm (Arm B), the differences were not clinically significant.

The results presented here demonstrate that the GEM plus CDDP combination is more effective than GEM alone against APCa at least in terms of median TTP and OR rate, whereas no differences were recorded in the CB rate or the median OS. Considering the natural history of this disease and the poor results obtained with the traditional treatments, the longer median TTP observed in our study, at least in our opinion, is quite an interesting result. The fact that there was no significant difference in median OS, despite the favorable trend registered in the combination arm, may be related to treatment withdrawal after 4 months of weekly administrations even in responding patients with a good PS. Furthermore, because the primary objective of the current study was to demonstrate an improvement in TTP, the size of the population enrolled clearly was not large enough to demonstrate any statistical advantage in terms of OS.

Data from the current study also confirmed that the CB response was not related to the objective response, as reported previously in other studies that employed GEM alone, especially when pain symptoms were considered. In patients with pancreatic carcinoma, pain is a consequence of tumor location rather than tumor bulk; therefore, even a small reduction in tumor size can lead to a significant CB improvement.

In conclusion, GEM plus CDDP on a weekly schedule was more active than single-agent GEM in patients with APCa in terms of TTP and overall response rates, with a low Grade 3–4 toxicity. Results concerning CB and OS rates, despite the favorable trend observed with the combination regimen, were not statistically different from the rates achieved with GEM alone. Therefore, this schedule may represent an optimal treatment for patients with advanced pancreatic carcinoma and may be used as a reference schedule when designing new regimens and for planning future Phase III trials.

REFERENCES

1. Evans DB, Abbruzzese JL, Rich TR. Cancer of the pancreas. In: De Vita VT Jr., Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology, 5th ed. Philadelphia: Lippincott, 1997:1054–87.
2. Palmer KR, Kerr M, Knowles G, Cull A, Carter DC, Leonard RCF, et al. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg* 1994;81:882–5.
3. Glimelius B, Hoffmann K, Sjoden P-O, Jacobsson G, Sellstrom H, Enader L-K, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996;7:593–600.
4. Ahlgren JD. Chemotherapy for pancreatic carcinoma. *Cancer* 1996;78(Suppl 1):654–63.
5. Smith FP, Hoth DF, Levin B, Karlin DA, MacDonald JS, Wolley PV, et al. 5-Fluorouracil, Adriamycin and mitomycin C (FAM) chemotherapy for advanced adenocarcinoma of the pancreas. *Cancer* 1980;46:2014–8.
6. Bitran JD, Desser RR, Kozloff MF, Billings AR, Shapiro CM. Treatment of metastatic pancreatic and gastric adenocarcinoma with 5-FU, Adriamycin and mitomycin (FAM). *Cancer Treat Rep* 1979;63:2049–51.
7. Wiggans RG, Wolley PV, Macdonald JS, Smythe T, Ueno W, Schein PS. Phase II trial of streptozotocin, mitomycin-C and 5-fluorouracil (SMF) in the treatment of pancreatic cancer. *Cancer* 1978;41:387–91.

8. Bukowski RM, Balcerzak SP, O'Bryan RM, Bonnet JD, Chenn TT. Randomised trial of 5FU and mitomycin C with or without streptozotocon for advanced pancreatic cancer. *Cancer* 1983;52:1577–82.
9. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin and mitomycin. *JAMA* 1985;253: 2061–7.
10. The Gastrointestinal Tumor Study Group. Phase II studies of drug combinations in advanced pancreatic carcinoma: fluorouracil plus doxorubicin plus mitomycin-C and two regimens of streptozotocin plus mitomycin plus fluorouracil. *J Clin Oncol* 1986;4:1794–8.
11. Oster MW, Gray R, Panasci L, Perry MC, for the Cancer and Leukemia Group B. Chemotherapy for advanced pancreatic cancer *Cancer* 1986;57:29–33.
12. Cullinan SA, Moertel CG, Wieand HS, Schutt AJ, Krook JA, Foley JP, et al. A Phase III trial on the therapy of advanced pancreatic carcinoma. *Cancer* 1990;65:2207–12.
13. Bruckner HW, Crown J, McKenna A, Hart R. Leucovorin and 5-fluorouracil as a treatment for disseminated cancer of the pancreas and unknown primary tumors. *Cancer Res* 1988; 48:5570–72.
14. Crown J, Casper ES, Botet J, Murray P, Kelsen DP. Lack of efficacy of high-dose leucovorin and fluorouracil in patients with advanced pancreatic adenocarcinoma. *J Clin Oncol* 1991;9:1682–6.
15. DeCaprio JA, Mayer RJ, Gonin R, Arbuck G. Fluorouracil and high-dose leucovorin in previously untreated patients with adenocarcinoma of the pancreas: results of a Phase II trial. *J Clin Oncol* 1991;9:2128–33.
16. Rubin J, Gallagher J, Schroeder G, Schutt AJ, Dalton RJ, Kugler JW, et al. Phase II trial of 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic gastric or pancreatic carcinomas. *Cancer* 1996;78:1888–91.
17. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC, et al. Evaluation of the antitumor activity of gemcitabine (2′2′-difluoro-2′-deoxycytidine). *Cancer Res* 1990;50:4417–22.
18. Huang P, Chubb S, Hertel LW, Grindey JB, Plumkett W. Action of 2′,2′-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 1991;52:6110–7.
19. Carmichael J, Fink U, Russel RCG, Spittle MF, Harris AL, Spiessi G, et al. Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer* 1996;73:101–5.
20. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, et al. Phase II trial of 2′,2′-difluorodeoxycytidine in patients with adenocarcinoma of the pancreas. *Invest New Drugs* 1994;12:29–34.
21. Crinó L, Mosconi AM, Calandri C, Corgna E, Darwish S, Tonato M. Gemcitabine in advanced pancreatic cancer: a Phase II trial [abstract 1266]. *Eur J Cancer* 1997;33(Suppl 8):S280.
22. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomised trial. *J Clin Oncol* 1997;15:2403–13.
23. Wils JA, Kok T, Wagener DJT, Selleslags J, Duez N. Activity of cisplatin in adenocarcinoma of the pancreas. *Eur J Cancer* 1993;29:203–4.
24. Kanzawa F, Saijo N. In vitro interaction between gemcitabine and other anticancer drugs using a novel three-dimensional model. *Semin Oncol* 1997;24(Suppl 7):S7-8–16.
25. Bergman AM, Ruiz van Haperen VWT, Veerman G, Kuiper CM, Peters GJ. Synergistic interaction between cisplatin and gemcitabine in vitro. *Clin Cancer Res* 1996;2:521–30.
26. Cardenal F, Lopez-Cabrerizo MP, Anton A, Alberola V, Massutti B, Carrato A, et al. Randomised Phase III study of gemcitabine-cisplatin in the treatment of locally advanced or metastatic non small cell lung cancer. *J Clin Oncol* 1991; 17:12–8.
27. Sandler A, Nemunaitis J, Denham C, Cormier J, von Pawel J, Niyikiza C, et al. Phase III study of cisplatin with or without gemcitabine in patients with advanced non small cell lung cancer [abstract 1747]. *Proc ASCO* 1998;17:454a.
28. Kaufman D, Raghavan D, Carducci M, Levine EG, Murphy B, Aisner J, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. *J Clin Oncol* 2000; 18:1921–7.
29. Moore MJ, Winquist E, Murray N, Tannock I, Huan S, Bennett K, et al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer. A Phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1999;17:2876–81.
30. Heinemann V, Wilke H, Possinger K, Mergenthaler H-G, Clemens M, Konig H, et al. Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. *Ann Oncol* 2000;11:1399–403.
31. Philip PA, Zalupski M, Vaitkevicius VK, Arlauskas P, Shields A. Phase II study of Gemcitabine and cisplatin in advanced or metastatic pancreatic cancer [abstract 1053]. *Proc ASCO* 1999;18:274a.
32. Traversa G, Maggini M, Menniti-Ippolito F, Bruzzi P, Chiarotti F, Greco D, et al. The unconventional Di Bella cancer treatment. A reflection on the Italian experience. The Italian Study Group for the Di Bella Multitherapy Trials. *Cancer* 1999;86:1903–11.
33. Storniolo AM, Enas NH, Brown CA, Voi M, Rothenberg ML, Schilsky R, et al. An investigational new drug treatment program for patients with gemcitabine. *Cancer* 1999;85: 1261–8.
34. Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Hitt R, et al. Phase I–II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J Clin Oncol* 1999;17:585–92.
35. Cascinu S, Silva RR, Barni S, Labianca R, Frontini L, Piazza E, et al. A combination of gemcitabine and 5-fluorouracil in advanced pancreatic cancer. A report from Group of the Studies of Digestive Tract Cancer (GISCAD). *Br J Cancer* 1999;80:1595–8.
36. Louvet C, Hammel P, André T, Vanica R, Landi B, Balosso J, et al. Multicenter Phase II study in advanced adenocarcinoma patients with a combination of leucovorin, 5FU bolus and infusion, and gemcitabine (FOLFUGEM regimen) [abstract 1054]. *Proc ASCO* 1999;18:275a.
37. Kakolyris S, Stathopoulos G, Tsavaris N, Andoulakis N, Kourousiss CH, Samantas E, et al. First line treatment with docetaxel and gemcitabine in patients with a advanced pancreatic cancer: a multicenter Phase II study [abstract 960]. *Proc ASCO* 1999;18:250a.
38. Scheithauer W, Kornek GV, Raderer M, Hejna M, Valencak J, Miholic J, et al. Phase II trial of gemcitabine, epirubicin and granulocyte-colony stimulating factor in patients with advanced pancreatic adenocarcinoma. *Br J Cancer* 1999;80: 1797–802.