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ORIGINAL REPORT

Randomized Phase III Trial of Gemcitabine Plus Cisplatin Compared With Single-Agent Gemcitabine As First-Line Treatment of Patients With Advanced Pancreatic Cancer: The GIP-1 Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
Single-agent gemcitabine became standard first-line treatment for advanced pancreatic cancer after demonstration of superiority compared with fluorouracil. The Gruppo Italiano Pancreas 1 randomized phase III trial aimed to compare gemcitabine plus cisplatin versus gemcitabine alone (ClinicalTrials.gov ID NCT00813696).

Patients and Methods
Patients with locally advanced or metastatic pancreatic cancer, age 18 to 75 years, and Karnofsky performance status (KPS) ≥ 50, were randomly assigned to receive gemcitabine (arm A) or gemcitabine plus cisplatin (arm B). Arm A: gemcitabine 1,000 mg/m^2 weekly for 7 weeks, and, after a 1-week rest, on days 1, 8, and 15 every 4 weeks. Arm B: cisplatin 25 mg/m^2 added weekly to gemcitabine, except cycle 1 day 22. Primary end point was overall survival. To have 80% power of detecting a 0.74 hazard ratio (HR) of death, with bilateral α .05, 355 events were needed and 400 patients planned.

Results
Four hundred patients were enrolled (arm A: 199; arm B: 201). Median age was 63, 59% were male, 84% had stage IV, and 83% had KPS ≥ 80. Median overall survival was 8.3 months versus 7.2 months in arm A and B, respectively (HR, 1.10; 95% CI, 0.89 to 1.35; $P = .38$). Median progression-free survival was 3.9 months versus 3.8 months in arm A and B, respectively (HR, 0.97; 95% CI, 0.80 to 1.19; $P = .80$). The objective response rate was 10.1% in A and 12.9% in B ($P = .37$). Clinical benefit was experienced by 23.0% in A and 15.1% in B ($P = .057$). Combination therapy produced more hematologic toxicity, without relevant differences in nonhematologic toxicity.

Conclusion
The addition of weekly cisplatin to gemcitabine failed to demonstrate any improvement as first-line treatment of advanced pancreatic cancer.

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INTRODUCTION

The majority of patients with pancreatic cancer are diagnosed in the advanced, unresectable stage, when the primary goals of treatment are survival prolongation and symptom palliation. The impact of systemic treatments in these patients is poor. Administration of gemcitabine is associated with some clinical benefit (CB) and a modest improvement in survival compared with fluorouracil.[1] Single-agent gemcitabine is currently recommended as standard first-line chemotherapy for patients with advanced disease.[2]

The combination of gemcitabine and cisplatin is supported by several preclinical data.[3-6] Gemcitabine increases cisplatin-induced DNA lesions and inhibits their repair, and cisplatin enhances the incorporation of gemcitabine triphosphate into DNA, inducing apoptosis of cancer cells. In a randomized trial published in 2002[7] by the Gruppo Oncologico Italia Meridionale (GOIM), 107 patients with locally advanced or metastatic pancreatic cancer were randomly assigned to single-agent gemcitabine or the combination of gemcitabine and cisplatin, in a weekly schedule. The combination significantly improved objective response rate (ORR) and time to

progression (TTP) compared with gemcitabine alone. CB rate was similar, and overall survival (OS) was longer with the combination, although the difference was not statistically significant.

These results were considered interesting but limited by the small number of patients, and three Italian cooperative groups (GOIM; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente [GISCAD]; Gruppo Oncologico Italiano di Ricerca Clinica [GOIRC]) decided to perform an Intergroup phase III trial, to compare the combination of gemcitabine and cisplatin, administered in the same schedule tested in the GOIM trial,[7] with single-agent gemcitabine. The aim of the Gruppo Italiano Pancreas (GIP) -1 study was to demonstrate a significant improvement in OS, chosen as primary end point.

PATIENTS AND METHODS

The GIP-1 protocol was approved by ethical committees at each participating Institution. All patients gave written informed consent before starting study procedures.

Patient Selection

Patients age 18 to 75 years with histologic or cytologic diagnosis of pancreatic cancer, stage II (if unresectable) or III or IV according to International Union against Cancer 1997 staging system,[8] Karnofsky performance status (KPS) $\geq$ 50, and who had not received prior chemotherapy were eligible. Other eligibility criteria included: adequate hematology (absolute neutrophil count $\geq$ 2,000/μL, platelets $\geq$ 100,000/μL, hemoglobin $\geq$ 10 g/dL), and biochemistry (serum creatinine $\leq$ upper normal limit [UNL], AST and ALT $\leq$ 2.5 $\times$ UNL, and bilirubin $\leq$ 1.5 $\times$ UNL, unless due to liver metastases). Presence of brain metastases and history of other invasive malignancy in previous 5 years were exclusion criteria.

Before random assignment, complete history and physical examination, routine hematology and biochemistry, ECG, chest x-ray, abdominal computed tomography (CT) scans, assessment of CB measures, and compilation of quality of life (QoL) questionnaires were required.

Study Treatments

Eligible patients were randomly assigned to arm A (standard treatment) or arm B (experimental treatment).

In arm A, gemcitabine was administered as 30-minute intravenous infusion, 1,000 mg/m^2, weekly for 7 consecutive weeks (cycle 1), followed by 1 week of rest. Thereafter, gemcitabine was continued on days 1, 8, and 15 every 28 days.

In arm B, gemcitabine was administered as in arm A. Cisplatin was administered, 25 mg/m^2, 1 hour before gemcitabine, on days 1, 8, 15, 29, 36, and 42 of cycle 1. On day 22, only gemcitabine was administered. Thereafter, after 1 week of rest, treatment was continued with both drugs on days 1, 8, and 15 every 28 days.

Before each administration, the following criteria had to be met: absolute neutrophil count $\geq$ 1,000/μL, platelets $\geq$ 100,000/μL, and absence of grade $\geq$ 2 nonhematologic toxicity. Without these conditions, treatments were postponed by 1 week and eventually stopped if minimum treatment conditions were still not met after 2 consecutive delays. Dose reductions were planned according to severity of hematologic toxicity.

No maximum number of cycles was planned, and patients continued treatment until disease progression, refusal, or unacceptable toxicity. Patients with disease progression could also continue treatment if they were experiencing CB. Second-line treatment was not defined by protocol, and was at investigator's discretion.

Study Evaluations

During treatment, CBC, serum creatinine, AST, and ALT were repeated weekly in both arms. Complete biochemistry and ECG were repeated at the end of each cycle. Toxicity was coded according to National Cancer Institute Common Toxicity Criteria version 2.0.

ORR was categorized according to Response Evaluation Criteria in Solid Tumors.[9] ORR was assessed at the end of cycle 1 in both arms, repeating chest x-ray and abdominal CT scan. All instrumental exams were read by investigators at each center. Confirmation of response was not required.

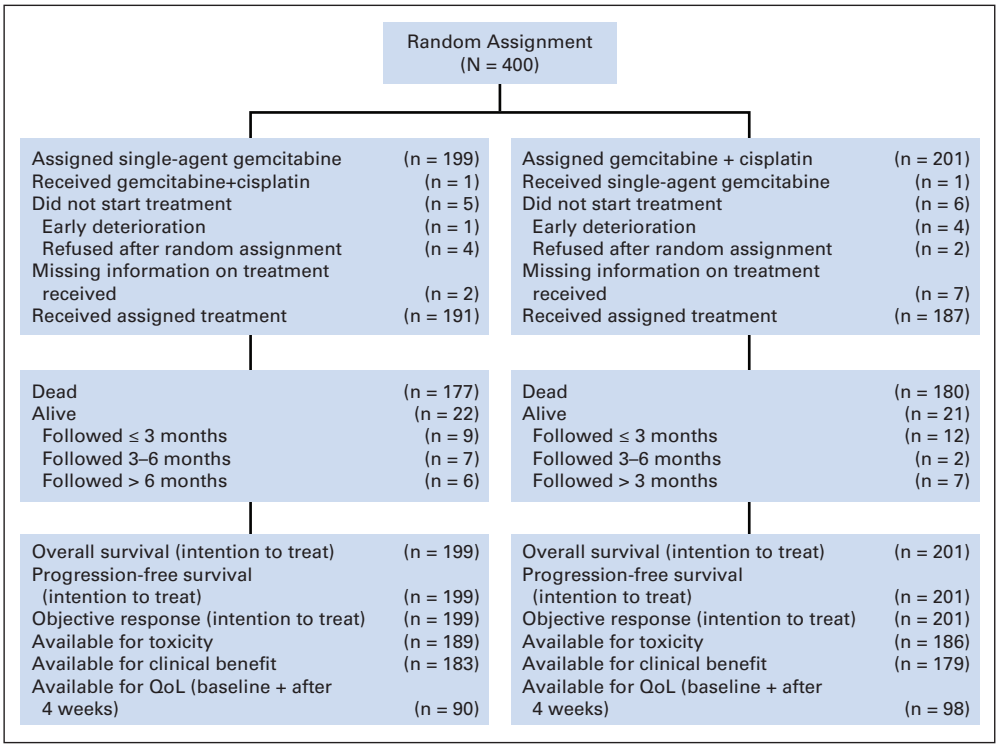

Fig 1. Flow of data collection according to CONSORT diagram.

CB rate was calculated measuring pain, functional impairment and weight loss, according to a previously described algorithm.[1] Pain (assessed by pain intensity and analgesic consumption) and functional impairment (assessed by KPS) represented primary measures. Weight change was a secondary measure. Pain intensity was recorded daily, the other parameters were assessed weekly. KPS was assessed by two independent observers. Each patient was classified as either positive, stable, or negative for each of the primary measures. Patients who were stable on both primary measures were classified as either responder or nonresponder based on weight. For patients to achieve an overall rating of positive CB, they had to be positive for at least one parameter without being negative for any of the others. This improvement had to last for at least 4 consecutive weeks.

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (version 3.0)[10] and PAN26[11] questionnaires were used to evaluate QoL. PAN26 is specific for pancreatic cancer patients.[11] Most items of the EORTC questionnaires refer to the week preceding administration. Both questionnaires are designed to be completed by the patient. EORTC questionnaires were completed at baseline (before random assignment) and every 4 weeks, up to six questionnaires, in both arms.

Study Design

GIP-1 was a open-label, randomized phase III study. The primary end point was OS. Secondary end points included progression-free survival (PFS), ORR, treatment toxicity, CB, and QoL.

Overall, 400 patients were planned and 355 deaths were required to have 80% power of detecting a 0.74 hazard ratio (HR) of death, with two-tailed α .05 (EAST; Cytel Software, Cambridge, MA). This would represent an increase in proportion of patients alive at 1 year from 18% to 28%, corresponding to an increase in median OS from 4.8 to 6.5 months. One interim analysis was planned, to be performed 3 to 4 months after the accrual of 200 patients, using an α spending function,[12] based on an O'Brien Fleming[13] sequential group design. Interim analysis was performed by the study statistician (C.G.), with blinded treatment labels. Investigators were only informed that accrual remained open.

Patients were randomly assigned to standard arm or experimental arm in a 1:1 ratio. Telephone random assignment was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy), by a computer-driven minimization procedure. Stratification factors were center, KPS (≥ 70 *v* ≤ 80), and stage (II-III *v* IV).

Data Analysis

Efficacy analyses were done on an intention-to-treat (ITT) basis. OS was defined as the interval between date of random assignment and date of death (or date of last follow-up for alive patients). PFS was defined as the interval between date of random assignment and date of progression or death whichever occurred first, or date of last follow-up for patients alive and without progression. Median follow-up was calculated according to the inverted Kaplan-Meier technique.[14] OS and PFS curves were estimated by Kaplan-Meier product limit method[15] and compared by log-rank test.[16] For OS, Cox proportional hazards model[17] was used to assess treatment effect after adjustment by baseline prognostic variables.

ORR was defined as the proportion of complete and partial responses on the total number of patients assigned to each arm. Patients who died or stopped treatment because of toxicity or refusal before restaging were conservatively defined as nonresponders. The statistical significance of the difference between ORRs in the two arms was assessed by χ^2 test.

All patients who received at least one chemotherapy administration were eligible for toxicity analysis. The worst grade of toxicity experienced throughout the treatment was computed for each patient. For each toxicity, two statistical tests were performed to assess the differences between arms: patterns of toxicity (considering all the possible grades) were compared by an exact linear rank test, while rates of severe toxicity (grade ≥ 3 *v* 0 to 2) were compared by χ^2 or Fisher's exact test as appropriate.

CB rate was defined as the proportion of responders on the number of patients with information available in each arm.

QoL analysis was performed according to EORTC manual.[18] Multi-item scales were computed by calculating the mean raw scores of single items and transforming them linearly so that all scales range from 0 to 100. For single items, only linear transformation was performed. For this article, only changes from baseline after 4 weeks were calculated for each domain and compared between arms, using baseline values as a covariate.

Statistical analyses were performed using S-Plus version 6.1 (Insightful Corp, Seattle, WA). Exact tests were performed using StatXact 7 (Cytel Software, Cambridge, MA).

RESULTS

Patient Characteristics

The CONSORT diagram of the trial is reported in Figure 1. Between April 2002 and April 2007, 400 patients were randomly assigned. Baseline characteristics were well balanced between arms (Table 1). Median age was 63 years, 59% of patients were male, 83% had KPS $\geq$ 80%, and 84% had stage IV disease. Most of the patients had adenocarcinoma, and 26% had received previous surgery.

Treatment Compliance

Information on treatment actually received was not available for nine patients (Fig 1). Of the remaining 391, 11 patients did not start treatment, five in arm A and 6 in arm B.

Table 1. Baseline Characteristics of Randomly Assigned Patients

Characteristic	Gemcitabine (n = 199)		Gemcitabine + Cisplatin (n = 201)		Overall (n = 400)	
	No.	%	No.	%	No.	%
Sex						
Male	113	56.8	125	62.2	238	59.5
Female	86	43.2	76	37.8	162	40.5
Median age, years	63		63		63	
Range	37-75		35-75		35-75	
Karnofsky performance status						
$\leq$ 70	33	16.6	36	17.9	69	17.3
$\geq$ 80	166	83.4	165	82.1	331	82.7
Stage						
II	9	4.5	6	3.0	15	3.8
III	24	12.1	25	12.4	49	12.2
IV	165	82.9	170	84.6	335	83.8
Missing information	1	0.5	—	—	1	0.2
Location of pancreatic tumor						
Head	91	45.7	101	50.2	192	48.0
Body	52	26.1	34	16.9	86	21.5
Tail	26	13.1	20	9.9	46	11.5
Head + body	10	5.0	6	3.0	16	4.0
Body + tail	18	9.0	39	19.4	57	14.3
Head + body + tail	1	0.5	1	0.5	2	0.5
Missing information	1	0.5	—	—	1	0.2
Histology						
Undefined	31	15.6	27	13.4	58	14.5
Adenocarcinoma	161	80.9	170	84.6	331	82.7
Squamous	1	0.5	1	0.5	2	0.5
Cystoadenocarcinoma	5	2.5	2	1.0	7	1.8
Missing information	1	0.5	1	0.5	2	0.5
Previous surgery						
No	152	76.4	145	72.1	297	74.3
Yes	47	23.6	56	27.9	103	25.7

Table 2. Cox Proportional Hazards Model: Overall Survival

Parameter	Hazard Ratio	95% CI	P
Treatment (GemCis *v* gem)	1.10	0.89 to 1.35	.39
Sex (female *v* male)	1.02	0.82 to 1.28	.86
Age (≥ 65 *v* < 65 years)	0.89	0.72 to 1.12	.32
Karnofsky PS (≥ 80 *v* ≤ 70)	0.71	0.54 to 0.93	**.01**
Stage (IV *v* II-III)	1.82	1.34 to 2.47	**.0001**
Previous surgery (yes *v* no)	0.86	0.67 to 1.10	.22

NOTE. Bold font indicates statistical significance.
Abbreviations: GemCis, gemcitabine + cisplatin; Gem, gemcitabine; PS, performance status.

The median number of chemotherapy administrations was eight (range, one to 37) and seven (range, one to 31), in arms A and B, respectively. Median total dose of gemcitabine was 7,390 mg/m^2 in arm A (range, 920 to 31,000 mg/m^2) and 7,000 mg/m^2 in arm B (range, 980 to 28,000 mg/m^2; $P = .017$, Wilcoxon rank sum test). Median dose intensity of gemcitabine was 784 mg/m^2/week (range, 296 to 1,067 mg/m^2/week), corresponding to 95% of the planned dose intensity, and 712 mg/m^2/week (range, 333 to 1,000 mg/m^2/week), corresponding to 83% of the planned dose intensity, in arms A and B respectively ($P < .001$, Wilcoxon rank sum test). In arm B, median total dose of cisplatin was 150 mg/m^2 (range, 0 to 689 mg/m^2) and median dose intensity was 16.1 mg/m^2/week (range, 0 to 27.1 mg/m^2/week), corresponding to 83% of the planned dose intensity.

Treatment was stopped because of progression or death in 72% and 66%, because of toxicity or refusal in 12% and 20%, because of other or unspecified reason in 16% and 14% of the patients, in arms A and B, respectively.

Information about second-line treatment was available in 346 patients. Second-line treatment was received by 93 (53.1%) of 175 patients in arm A and 70 (40.9%) of 171 in arm B. Twenty patients (11.4%) in arm A received cisplatin-based second-line treatment; oxaliplatin alone or in combination was received by 29 patients (16.6%) and 21 patients (12.2%) in arms A and B, respectively. As expected, second-line treatment was received by patients who lived longer: median OS was 11.7 months for patients who received second line and 4.4 months for patients who did not.

Efficacy

All 400 patients were included in ITT analyses. At December 2008, with a median follow-up of 38.2 months, 357 deaths (89%) were recorded, 177 in arm A and 180 in arm B.

Median OS was 8.3 months for patients assigned to gemcitabine compared with 7.2 months for patients assigned to combination (HR, 1.10; 95% CI, 0.89 to 1.35, two-sided $P = .38$). At 1 year, 34.0% and 30.7% of patients were alive, in arms A and B respectively. At multivariate analysis, there are no significant differences between treatment arms (Table 2). OS curves are shown in Figure 2A. Exploratory survival analysis by subgroups according to sex, age, stage, KPS, and previous surgery is shown in Figure 3; no heterogeneity of treatment effect around the overall effect is apparent among subgroups.

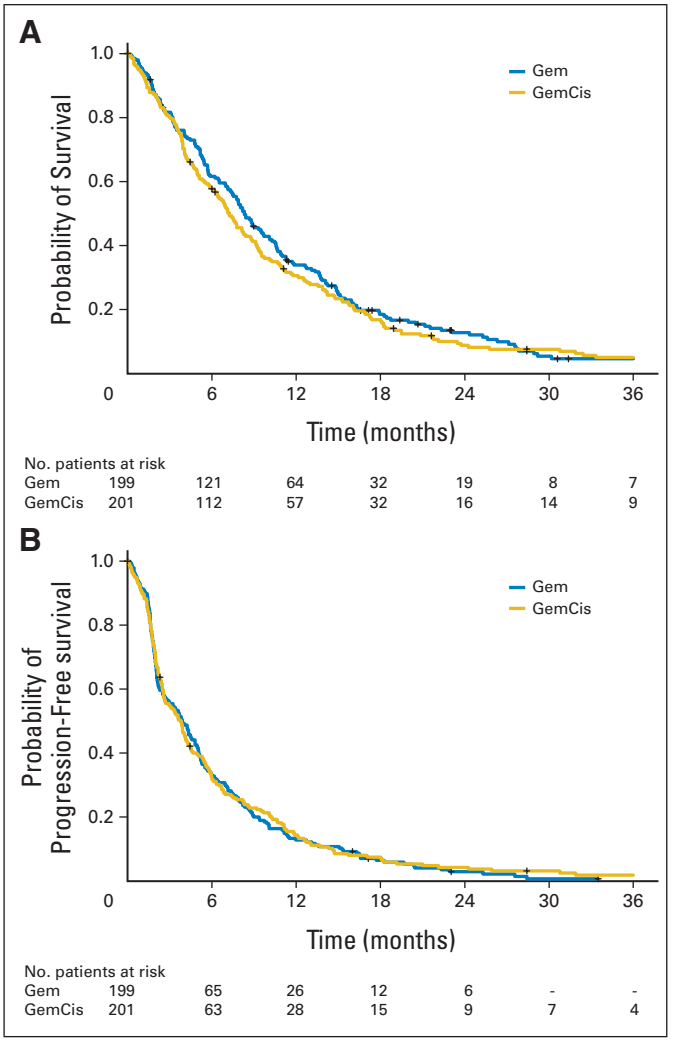

Fig 2. (A) Overall survival and (B) progression-free survival curves by treatment arm. Gem, gemcitabine; GemCis, gemcitabine + cisplatin.

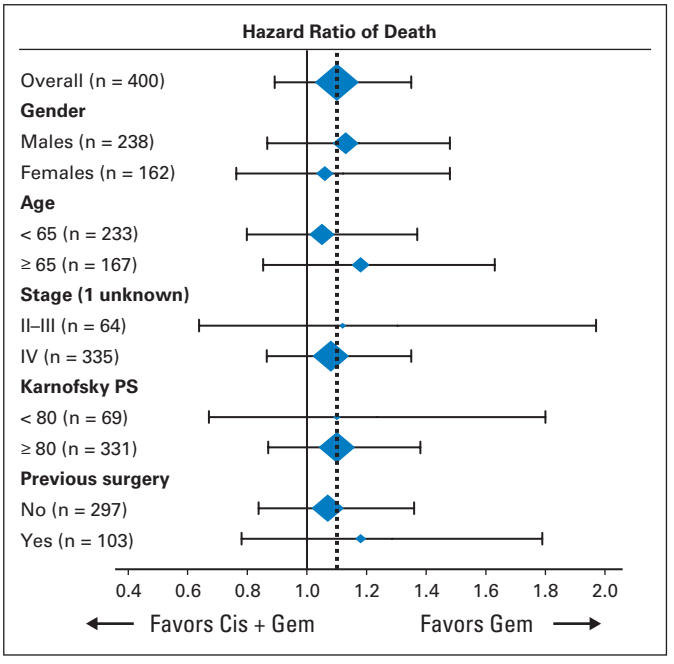

Fig 3. Treatment effect on overall survival within major patient subgroups. Vertical dotted line represents hazard ratio (gemcitabine [Gem] + cisplatin [Cis] *v* Gem) in the overall population.

With 382 progressions recorded (96%), median PFS was 3.9 and 3.8 months, in arms A and B, respectively (HR, 0.97; 95% CI, 0.80 to 1.19; two-sided $P = .80$). At 1 year, 12.8% and 14.5% of patients were progression free, in arms A and B, respectively. PFS curves are shown in Figure 2B.

Patients assigned to single-agent gemcitabine had complete response in 1.0% and partial response in 9.0%, for an ORR of 10.1% (95% CI, 6.6% to 15.0%). Patients assigned to combination had complete response in 1.5% and partial response in 11.4%, for an ORR of 12.9% (95% CI, 9.0% to 18.3%). ORR was not significantly different between arms ($P = .37$).

Toxicity

All patients with information on treatment who received at least one dose of chemotherapy were considered eligible for toxicity analysis (n = 380). Information about toxicity was missing for three patients (two in arm A, one in arm B). Two further patients were excluded (one in each arm) because they actually received the other treatment. The worst toxicity experienced by the remaining 375 patients is summarized in Table 3.

Hematologic toxicity was more frequent and severe with combination chemotherapy. Patients assigned to the experimental arm experienced more anemia (all grades: 51% *v* 39%, grade 3: 5% *v* 1%), more neutropenia (all grades: 45% *v* 36%, grade 3-4: 25% *v* 14%), and more thrombocytopenia (all grades: 58% *v* 30%, grade 3-4: 16% *v* 5%). No relevant differences were seen in nonhematologic toxicity.

There were five deaths potentially related to the treatment, two with gemcitabine (one stroke, one gastrointestinal bleeding) and three with combination chemotherapy (one deep venous thrombosis, one sudden death, one death for unknown reason in patient with severe thrombocytopenia).

CB

Information about CB was available for 362 patients (91%). Details of CB analysis are reported in Appendix Table A1 (online only). Overall CB responders were 23.0% of patients in arm A and 15.1% in arm B ($P = .057$).

QoL

Overall, 334 patients (161 arm A *v* 173 arm B) completed baseline QoL questionnaire. Of these, 188 completed the second questionnaire after 4 weeks (90 arm A *v* 98 arm B) and were eligible for this analysis. After 4 weeks, mean difference from baseline in global QoL (EORTC

Table 3. Worst Grade of Toxicity According to Treatment Arm

	NCI-CTC Grade																							
	Gemcitabine (n = 189)												Gemcitabine + Cisplatin (n = 186)											
	0		1		2		3		4		5		0		1		2		3		4		5			
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P**	*P*†
Anemia	115	61	39	21	33	17	2	1	—	—	—	—	91	49	38	20	48	26	9	5	—	—	—	—	**.005**	**.03**
Leukopenia	136	72	19	10	26	14	6	3	2	1	—	—	127	68	18	10	27	15	13	7	1	< 1	—	—	.35	.17
Neutropenia	121	64	20	11	22	12	22	12	4	2	—	—	102	55	16	9	22	12	35	19	11	6	—	—	**.02**	**.007**
Febrile neutropenia	188	99					1	< 1	—	—	—	—	186	100					—	—	—	—	—	—	1.00	1.00
Neutropenic infection	189	100											186	100											—	—
Non-neutropenic infection	186	98	1	< 1	2	1	—	—	—	—	—	—	186	100	—	—	—	—	—	—	—	—	—	—	0.25	—
Thrombocytopenia	133	70	33	17	13	7	10	5	—	—	—	—	78	42	38	20	41	22	22	12	7	4	—	—	**< .001**	**.001**
Allergy	188	99	1	1	—	—	—	—	—	—	—	—	186	100	—	—	—	—	—	—	—	—	—	—	1.00	—
Kidney	189	100	—	—	—	—	—	—	—	—	—	—	182	98	4	2	—	—	—	—	—	—	—	—	.06	—
Heart, rhythm	187	99	1	< 1	—	—	1	< 1	—	—	—	—	182	98	2	1	1	< 1	1	< 1	—	—	—	—	.15	1.00
Heart, general (CV)	189	100	—	—	—	—	—	—	—	—	—	—	183	98	1	< 1	1	< 1	—	—	—	—	1	< 1	.12	.50
Fatigue	112	59	39	21	32	17	6	3	—	—	—	—	111	60	23	12	42	23	10	5	—	—	—	—	.56	.29
Fever	161	85	20	11	8	4	—	—	—	—	—	—	163	88	15	8	7	4	1	< 1	—	—	—	—	.53	.50
Weight loss	172	91	11	6	5	3	1	< 1	—	—	—	—	164	88	15	8	6	3	1	< 1	—	—	—	—	.38	1.00
Hair loss	188	99	1	< 1	—	—							174	94	5	3	7	4							**.0008**	NA
Skin	187	99	1	< 1	1	< 1	—	—	—	—	—	—	185	99	1	< 1	—	—	—	—	—	—	—	—	.87	—
Anorexia	166	88	14	7	8	4	1	< 1	—	—	—	—	151	81	18	10	13	7	4	2	—	—	—	—	.07	.21
Constipation	157	83	19	10	10	5	2	1	1	< 1	—	—	157	84	16	9	9	5	4	2	—	—	—	—	.75	.72
Diarrhea	173	92	8	4	5	3	3	2	—	—	—	—	163	88	12	6	10	5	—	—	1	< 1	—	—	.23	.62
Nausea	120	63	45	24	22	12	2	1	—	—	—	—	115	62	39	21	27	15	5	3	—	—	—	—	.53	.28
Vomiting	154	81	19	10	15	8	1	< 1	—	—	—	—	144	77	22	12	15	8	5	3	—	—	—	—	.31	.12
Stomatitis	179	95	7	4	3	2	—	—	—	—	—	—	174	94	7	4	3	2	2	1	—	—	—	—	.55	.25
Liver	145	77	14	7	16	8	10	5	4	2	—	—	159	85	9	5	8	4	7	4	3	2	—	—	**.03**	.42
Neuropathy	188	99	1	< 1	—	—	—	—	—	—	—	—	181	97	1	< 1	2	1	2	1	—	—	—	—	.06	.25
Other	167	88	4	2	6	3	7	4	3‡	2	2§	1	165	89	6	3	6	3	6	3	1‖	< 1	2¶	1	.87	.53

NOTE. Bold font indicates statistical significance.
Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; CV, cardiovascular; NA, not applicable.
*Any grade, tested for trend.
†Severe (grade 3 or higher).
‡Two grade 4 hyperglycemia; 1 grade 4 hypokaliemia.
§One grade 5 stroke, 1 grade 5 GI bleeding.
‖One grade 4 hyper-gamma GT.
¶One death for unknown reason 7 days after G4 thrombocytopenia, one sudden death.

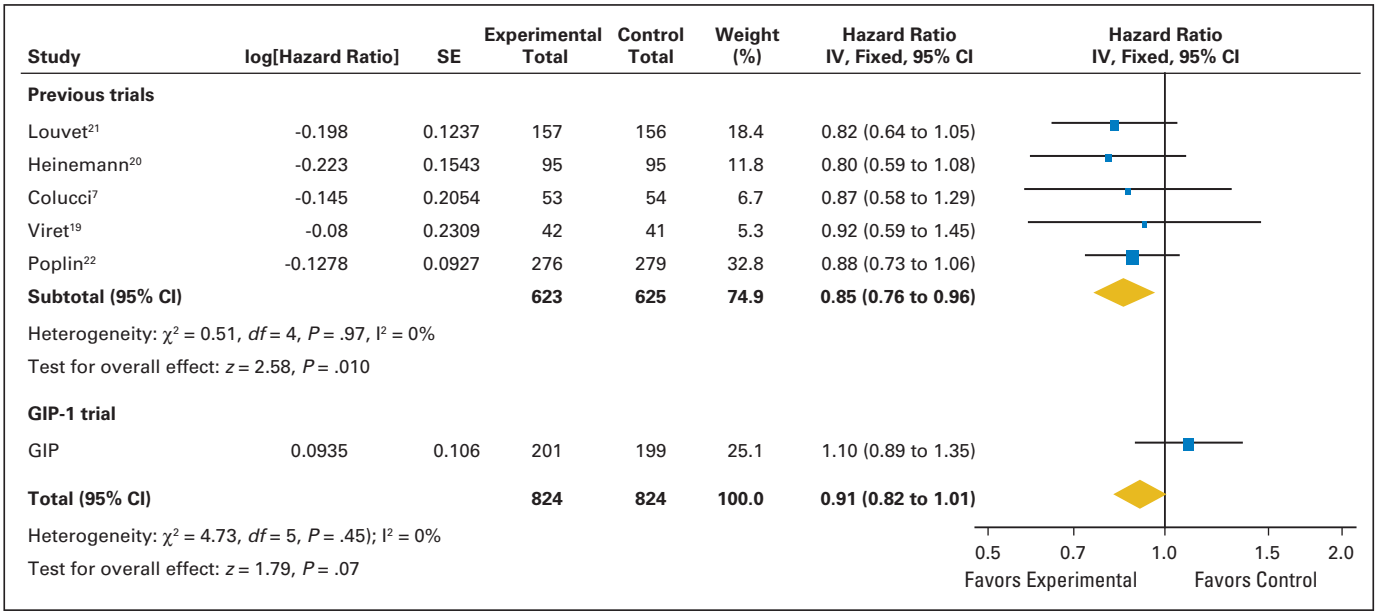

Fig 4. Updated meta-analysis of randomized trials comparing gemcitabine + platinum compound versus gemcitabine in advanced pancreatic cancer. IV, inverse variance; df, degrees of freedom.

C30, items 29-30) was 6.20 in arm A and 0.09 in arm B. This difference was not statistically significant ($P = .07$). Statistically significant differences were reported in social functioning and limitation in planning, both favoring single-agent gemcitabine, and in hepatic symptoms, favoring combination.

DISCUSSION

In this phase III trial, the addition of cisplatin to gemcitabine for patients with advanced pancreatic cancer failed to show any advantage. Improvement in OS, the primary end point, was not obtained, and there was no benefit in terms of PFS, ORR, CB, and QoL. Hematologic toxicity was higher with the addition of cisplatin. Nonhematologic toxicity, on the contrary, was similar between arms. The schedule adopted, characterized by weekly doses of cisplatin, was not associated with significant emesis or other typical effects of higher doses. The addition of cisplatin, however, was associated with a statistically significant reduction in the dose intensity of gemcitabine.

The cisplatin schedule adopted in this study was based on the previous GOIM trial.[7] In that small trial, the combination produced a significant increase in ORR and TTP, compared to single-agent gemcitabine, without significant prolongation of OS. After the start of GIP-1, two other trials testing the addition of cisplatin to gemcitabine in patients with advanced pancreatic cancer have been published, although with different cisplatin dose and schedule.[19,20] In a small French trial, cisplatin 75 mg/m^2 every 4 weeks added to gemcitabine did not demonstrate significant benefit.[19] In the larger German trial, enrolling 195 patients, subjects in experimental arm received gemcitabine 1,000 mg/m^2 and cisplatin 50 mg/m^2 on days 1 and 15 of a 4-week cycle.[20] Combination chemotherapy was associated with a statistically significant prolongation of PFS. Median OS was longer with combination (7.5 *v* 6.0 months), but the difference was not statistically significant. Furthermore, two randomized trials testing the addition of oxaliplatin to gemcitabine did not demonstrate a statistically significant prolongation in OS.[21,22]

All these trials had a sample size considered too small to demonstrate potentially relevant differences in survival. With this aim, several pooled analyses and meta-analyses have been performed.[23-26] In the meta-analysis by Heinemann, [23] pooling the above cited five trials that added oxaliplatin or cisplatin, the platin-based combination treatment was associated with a significant improvement in OS (HR, 0.85; 95% CI, 0.76 to 0.96; $P = .01$). We updated the meta-analysis including GIP-1 trial, adding 400 to the previous 1,248 patients (Fig 4). There was no statistical heterogeneity with the addition of GIP-1 to the five previous trials. Indeed, the addition of GIP-1 data produced a pooled HR of 0.91 (95% CI, 0.82 to 1.01). The pooled result is no longer statistically significant.

Other gemcitabine-based combinations have been tested. In a randomized phase III trial, the combination of gemcitabine and capecitabine produced a trend toward prolongation of OS,[27] but this advantage was not confirmed in another trial.[28] In recent years, phase III trials have tried to obtain a prolongation of survival using molecularly targeted agents.[29,30] A statistically significant OS benefit was obtained adding erlotinib to gemcitabine.[29] However, the small survival gain renders the clinical value of erlotinib debatable, and single-agent gemcitabine remains standard first-line treatment.

Subgroup analyses from several studies indicated that the benefit of gemcitabine-based combination chemotherapy in terms of OS is predominantly seen in patients with good KPS.[23,24,28] Although that finding should be considered only hypothesis generating, some guidelines consider combination chemotherapy a potential option for patients with good KPS.[2] Our data do not support this finding, and subgroup analysis shows no evidence of a differential effect of treatment in patients with KPS $\geq$ 80 versus KPS lower than 80. Also if patients, according to literature, are divided in good KPS ($\geq$ 90) versus poor KPS ($\leq$ 80), there is no evidence of interaction (data not shown).

In conclusion, the negative results of the GIP-1 trial add important evidence to the debate about the role of combination chemotherapy as first-line treatment of advanced pancreatic cancer. In this trial, the addition of weekly cisplatin to gemcitabine did not produce any benefit compared to single-agent gemcitabine. Prognosis of patients with advanced pancreatic cancer remains unacceptably poor. The best option for these patients remains enrollment in prospective clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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