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ORIGINAL REPORT

Irinotecan Plus Oxaliplatin and Leucovorin-Modulated Fluorouracil in Advanced Pancreatic Cancer—A Groupe Tumeurs Digestives of the Fédération Nationale des Centres de Lutte Contre le Cancer Study

Thierry Conroy, Bernard Paillot, Eric François, Roland Bugat, Jacques-Henri Jacob, Ulrich Stein, Salvador Nasca, Jean-Philippe Metges, Olivier Rixe, Pierre Michel, Emmanuelle Magherini, Aliette Hua, and Gael Deplanque

From Centre Alexis Vautrin, Nancy; University Hospital, Rouen; Centre Antoine Lacassagne, Nice; Centre Claudius Regaud, Toulouse; Centre François Baclesse, Caen; University Hospital Jean Minjoz, Besançon; Institut Jean Godinot, Reims; University Hospital, Brest; Clinique Claude Bernard, Metz; and Laboratoire Aventis, Paris, France.

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Address reprint requests to Thierry Conroy, MD, Department of Medical Oncology, Centre Alexis Vautrin, 54511 Vandoeuvre-lès-Nancy Cedex, France; e-mail: t.conroy@nancy.fnclcc.fr.

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ABSTRACT

Purpose
To evaluate response rate and toxicity of irinotecan and oxaliplatin plus fluorouracil (FU) and leucovorin (Folfirinox) in advanced pancreatic adenocarcinoma (APA).

Patients and Methods
Chemotherapy-naive patients with histologically proven APA and bidimensionally measurable disease were treated with Folfirinox therapy every 2 weeks, which comprised oxaliplatin 85 mg/m^2 and irinotecan 180 mg/m^2 plus leucovorin 400 mg/m^2 followed by bolus FU 400 mg/m^2 on day 1, then FU 2,400 mg/m^2 as a 46-hour continuous infusion. Quality of life (QOL) was assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).

Results
Forty-seven patients were entered, and 46 received treatment. Thirty-five patients (76%) had metastatic disease. A total of 356 cycles were delivered, with a median of eight cycles per patient (range, one to 24 cycles). All patients were assessable for safety. No toxic death occurred. Grade 3 to 4 neutropenia occurred in 52% of patients, including two patients with febrile neutropenia. Other relevant toxicities included grade 3 to 4 nausea (20%), vomiting (17%), and diarrhea (17%) and grade 3 neuropathy (15%; Levi's scale). The confirmed response rate was 26% (95% CI, 13% to 39%), including 4% complete responses. Median time to progression was 8.2 months (95% CI, 5.3 to 11.6 months), and median overall survival was 10.2 months (95% CI, 8.1 to 14.4 months). Between baseline and end of treatment, patients had improvement in all functional scales of the EORTC QLQ-C30, except cognitive functioning. Responders had major improvement in global QOL.

Conclusion
With a good safety profile, a promising response rate, and an improvement in QOL, Folfirinox will be further assessed in a phase III trial.

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INTRODUCTION

Pancreatic cancer ranks as the fourth leading cause of cancer deaths in the Western world. There are an estimated 30,000 deaths in the United States[1] and 50,000 deaths per year in Europe.[2] Because of the aggressiveness of pancreatic cancers and the lack of effective systemic therapies, only 1% to 4% of patients with adenocarcinoma of the pancreas will be alive 5 years after diagnosis.[1,3] Advanced pancreatic adenocarcinoma (APA) remains an incurable disease with few good treatment options. However, two randomized trials

demonstrated that chemotherapy improves both survival and quality of life (QOL) compared with best supportive care (BSC).[4,5] A randomized trial comparing gemcitabine with 30-minute infusion fluorouracil (FU) demonstrated a modest significant survival advantage for the gemcitabine group.[6] Several attempts at developing more efficacious gemcitabine-based regimens have been carried out, but despite encouraging results from phase II trials, randomized studies to date have not shown a survival benefit for combination chemotherapy over gemcitabine alone.[7-15] Therefore, new effective and well-tolerated regimens are warranted.

Irinotecan, a camptothecin analog, has been demonstrated to have a higher growth inhibitory effect against cultured pancreatic adenocarcinoma than cisplatin, mitomycin, and FU.[16] Preclinical studies have indicated a synergy when irinotecan precedes FU-leucovorin exposure.[17-19] Other studies have shown high activity of irinotecan on pancreatic tumor cells in culture and in xenografts.[20,21] Irinotecan has been investigated as a single agent in patients with nonpretreated APA, producing response rates from 9% to 27%.[22-24] Some activity as second-line chemotherapy has also been reported.[25,26]

Oxaliplatin, a platinum-based drug, also inhibits pancreatic tumor cell lines.[27] When used as a single agent, oxaliplatin has minimal activity against APA, but a 10% response rate has been described when it was used with FU.[28] In vitro, synergistic activity has been described between irinotecan and oxaliplatin.[29,30] Differences in mechanism of action of oxaliplatin and irinotecan, combined with the demonstrated antitumor activity of each agent, suggest that coadministration of oxaliplatin and irinotecan to patients with APA may provide clinical outcomes superior to those obtained with either drug administered alone. Furthermore, with the exception of myelosuppression and diarrhea, the two drugs have no overlapping clinical toxicity.

One previous phase I trial[31] evaluated a triplet combination of leucovorin plus bolus and continuous-infusion FU (LV5FU),[32] irinotecan, and oxaliplatin. The recommended doses were oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, and full doses of simplified LV5FU. Of five patients with APA, one complete response (CR) and one partial response (PR) were observed. On the basis of these encouraging results, a multicenter phase II study of the oxaliplatin and irinotecan plus LV5FU combination (Folfirinox) was conducted by the Gastrointestinal Tumor Group of the French Anticancer Centers. The main objectives were to assess the efficacy and safety of the Folfirinox combination as first-line treatment in patients with APA.

PATIENTS AND METHODS

Patients Selection

Eligible patients were required to have histologically or cytologically proven APA, unresectable locally advanced or metastatic disease, at least one bidimensionally measurable lesion according to WHO criteria,[33] no previous chemotherapy or radiotherapy, an age between 18 and 70 years, a WHO performance status (PS) less than 2, and adequate bone marrow, liver (total bilirubin $\leq 1.5 \times$ the upper limits of normal [ULN], AST and ALT $\leq 3 \times$ UNL, and alkaline phosphatases $< 3 \times$ ULN or $< 5 \times$ ULN in case of liver involvement), and renal function (creatinine $<$ 130 μmol/L). Surgical unresectability was defined by laparotomy or by multidisciplinary consultation looking at radiologic criteria as extrapancreatic disease or celiac or superior mesenteric artery involvement. Written informed consent was required, and the ethical committee approved the study. Patients with CNS metastases, second malignancies, and a history of chronic diarrhea, angina pectoris, National Cancer Institute Common Toxicity Criteria grade greater than 1 peripheral neuropathy, or psychiatric disorders were excluded.

Chemotherapy

Folfirinox consisted of oxaliplatin 85 mg/m^2 diluted in 5% dextrose administered as a 2-hour intravenous infusion followed by irinotecan 180 mg/m^2 administered as a 90-minute infusion in dextrose 5% 500 mL or normal saline 1 hour after the end of oxaliplatin infusion. The simplified LV5FU regimen was administered after the irinotecan infusion as follows: leucovorin 400 mg/m^2 over 2 hours followed by FU 400 mg/m^2 bolus, then FU 2,400 mg/m^2 was administered as a 46-hour continuous infusion. Treatment cycles were repeated every 2 weeks.

Antiemetic prophylaxis was left to investigator's discretion. In case of severe cholinergic syndrome, preventive treatment with atropine (0.25 mg subcutaneously) was to be administered at all subsequent cycles. If patients experienced delayed diarrhea, early high-dose loperamide was prescribed according to specific guidelines, and if diarrhea persisted more than 48 hours, prophylactic oral fluoroquinolones were administered. In case of severe neutropenia and/or no recovery to grade less than 1 at day 14, further cycles could be administered with a granulocyte colony-stimulating factor (G-CSF).

Patients were assessed for toxicity before each cycle. Chemotherapy was delayed until recovery if neutrophils were less than 1.5×10^9/L or platelets were less than 100×10^9/L. Doses adjustments were made according to nadir values and time of recovery to a grade ≤ 1. Doses reductions were also recommended in case of grade 3 to 4 diarrhea, stomatitis, hand and foot syndrome, and vomiting and/or in case of grade 2 peripheral neuropathy. For any other nonhematologic toxicity that occurred with grade ≥ 2, a maximum delay of treatment of 2 weeks was allowed to attempt recovery to grade ≤ 1. Once the dose was decreased, re-escalation was not permitted. Patients went off study if they required more than two dose reductions.

Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Twelve cycles were recommended in responding patients, and patients were observed every 3 months until death or cutoff date.

Efficacy Assessment

The primary efficacy end point was response rate, which was defined as the sum of CR and PR assessed according to WHO criteria.[33] CR was defined as the complete disappearance of all assessable disease, and PR was defined as a decrease of at least 50% of the sum of the products of the diameters of measurable lesions. Responses had to be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met.

Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in measurable lesions, and progressive disease was defined as an increase of at least 25% in measurable lesions or the appearance of new malignant lesion(s). Computed tomography scan imaging was performed at baseline and then every 6 weeks until disease progression. Patients who were withdrawn from study before the first evaluation were classified as having experienced treatment failure. All computed tomography scans were reviewed by an external response review committee (ERRC), which was a panel of two independent radiologists not involved in the study. Secondary efficacy end points included the duration of response and stabilization, time to progression, and overall survival. Time to progression was calculated from the start of treatment to the first day of progression. Survival lasted from the date of inclusion until death.

Safety Assessment

Patients who received at least one infusion were assessable for safety. For hematologic and biologic parameters, at least one measure per cycle was required. Toxic effects (except paresthesias) were graded using the National Cancer Institute Common Toxicity Criteria version 1.0. Peripheral sensitive neuropathy was graded according to Levi's specific grading.[34]

QOL and Clinical Benefit Assessment

QOL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30, version 3.0). The EORTC QLQ-C30 is a 30-item questionnaire including five functional scales, three symptom scales, one QOL scale, and six single items on common symptoms.[35] The EORTC QLQ-C30 questionnaire was distributed to the patients before each cycle and at the end of the treatment. Questionnaires were scored according to the EORTC instructions.[36] Baseline and last available questionnaires were compared. The primary objective was to analyze changes in global QOL, and secondary objectives were to describe changes in fatigue, pain, physical functioning, and emotional functioning. These scales were chosen because they are the most deteriorated in APA patients according to the EORTC reference values manual.[37] Clinical benefit response was evaluated according to assessment of consumption of pain-relieving drugs, weight trends, or evolution of asthenia or anorexia.

Statistical Considerations

According to a Simon two-stage phase II optimal design[38] for a goal of 25% true response rate with an α and β error probability of .05 and .20, respectively, an accrual of at least 40 eligible patients assessable for response was planned. Assuming that 15% of patients would be inassessable, 46 patients needed to be included. An early termination of the study was required if less than three responses were observed in the first 22 patients. Otherwise, recruitment continued. The 95% CI for response was calculated. Time-related parameters, including median follow-up time, were analyzed using the Kaplan-Meier method.[39,40]

RESULTS

Patient Characteristics

From June 2000 to June 2002, 47 patients were enrolled at nine French centers. One patient was never treated because of sudden onset of icterus. The baseline characteristics of the 46 treated patients are listed in Table 1. The median age was 56 years (range, 40 to 69 years), and 76% of patients had stage IVb disease at diagnosis. Among 11 patients with locally advanced disease, two patients had celiac artery involvement, one patient had local recurrence, and eight patients had unresectable tumor assessed during explorative laparotomy. Thirty-four patients (74%) had an impaired PS, and 39 patients (85%) were suffering at least from one disease-related symptom at study entry.

Study Treatment and Drug Delivery

A total of 356 cycles were completed (median, eight cycles per patient; range, one to 24 cycles). Doses reductions were required in 50 cycles (14%), and the main reasons for dose reduction were hematologic toxicity, neurotoxicity, and diarrhea (Table 2). Short treatment delays (< 7 days) occurred in 48 cycles (13%), and longer delays (> 7 days) occurred in 66 cycles (19%). Those delays were mainly a

Table 1. Characteristics of Treated Patients

	No. of Patients	%
Sex		
Male	30	65
Female	16	35
Age, years		
Median	56	
Range	40-69	
WHO performance status		
0	12	26
1	34	74
Disease stage		
Stage III/IVa	11	24
Stage IVb	35	76
Prior surgery		
None	23	50
Curative resection	2	4
Explorative laparotomy	9	20
Palliative surgery	12	26
No. of sites involved*		
1	6	13
2	19	41
3	13	28
≥ 4	8	17
Disease localization		
Pancreas	45	98
Liver	28	61
Lymph nodes	24	52
Peritoneum	11	24
Lung	4	9
Other†	2	4
Signs and symptoms		
Weight loss $\geq 5\%$	30	65
Disease-related pain	32	70
Asthenia	16	35
Anorexia	16	35

*Including abdominal lymph nodes.
†One patient with ovarian metastases and one with ascitis.

Table 2. Drug Delivery

Drug Delivery	Values
Total No. of cycles	356
No. of cycles per patient	
Median	8
Range	1-24
Relative dose-intensity per patient, %	
Oxaliplatin	
Median	82
95% CI	35 to 103
Irinotecan	
Median	84
95% CI	38 to 101
Fluorouracil bolus	
Median	83
95% CI	6 to 101
Continuous fluorouracil	
Median	83
95% CI	40 to 101
Cycles with dose reductions	
No.	50
%	14
Responsible drug for dose reductions	
Oxaliplatin	
No. of cycles	24
%	7
Irinotecan	
No. of cycles	22
%	6
Fluorouracil	
No. of cycles	21
%	6
Main reason for reduction	
Hematologic toxicity	
Oxaliplatin	
No. of cycles	9
%	38
Irinotecan	
No. of cycles	8
%	36
Fluorouracil	
No. of cycles	16
%	76
Neurotoxicity	
Oxaliplatin	
No. of cycles	12
%	50
Diarrhea	
Irinotecan	
No. of cycles	9
%	41
Fluorouracil	
No. of cycles	1
%	5
Delayed cycles	
Total	
No.	114
%	32
Because of hematologic toxicity	
No.	76
%	67
Delayed between 4 and 7 days	
No.	48
%	13
Delayed more than 7 days	
No.	66
%	19

result of at least one hematologic toxicity (76 cycles, 67%). In 25 cycles (22%), delays were unrelated to study treatment. The delivered relative dose-intensity per patient was 82% for oxaliplatin, 84% for irinotecan, and 83% for FU.

Objective Response and Survival

Response rate was evaluated in all treated patients. After the first 22 assessable patients were treated, four confirmed objective responses were observed and, thus, accrual could continue. Overall results are listed in Table 3. Twelve PRs (26%) and 18 stabilizations (39%) were observed by the investigators, resulting in an overall response rate of 26% (95% CI, 13% to 39%). Three (27.3%) of 11 patients with local APA and nine of 35 patients with metastatic disease achieved a confirmed response. This was confirmed by the ERRC, with two CRs (4%), 10 PRs (22%), and 16 patients with stable disease (35%). With a median follow-up of 33 months, the median response duration was 10.4 months (95% CI, 9.0 to 15.2 months), and median progression-free

Table 3. Efficacy Results (N = 46)

Response	Assessed by an Independent Review	Assessed by the Investigators
Objective response rate		
No.	12	12
%	26	26
95% CI, %	13 to 39	13 to 39
Response duration, months		
Median	9.3	10.4
95% CI	8.2 to 13.6	9.0 to 15.2
Time to progression, months		
Median	8.2	5.6
95% CI	5.3 to 11.6	3.4 to 9.0
Survival, months		
Overall		
Median	10.2	
95% CI	8.1 to 14.4	
Metastatic patients		
Median	9.5	
95% CI	5.6 to 13.7	
Locally advanced patients		
Median	15.7	
95% CI	8.9 to 43	
Symptom benefit		
Increase of weight, n = 46		
No.	12	
%	26	
Decrease in anorexia, n = 27		
No.	8	
%	30	
Decrease in fatigue, n = 19		
No.	4	
%	21	
More than 50% decrease in analgesic consumption, n = 39		
No.	9	
%	23	

survival (PFS) was 5.6 months (95% CI, 3.4 to 9.0 months) according to the investigators. According to the ERRC, median response duration was 9.3 months (95% CI, 8.2 to 13.6 months), median PFS was 8.2 months (95% CI, 5.3 to 11.6 months), and median duration of stable disease was 7.5 months (95% CI, 5.1 to 15.1 months). When tumor progressed, 31 patients (67%) received a second-line treatment, including gemcitabine (n = 18), radiochemotherapy (n = 4), Folfiri (irinotecan, bolus- and continuous-infusion FU; n = 3), gemcitabine and oxaliplatin (n = 1), Folfox (oxaliplatin, bolus- and continuous-infusion FU; n = 1), and FU-leucovorin (n = 1). After having stopped chemotherapy, three patients who responded to Folfirinox received Folfirinox again when they progressed.

Median overall survival was 10.2 months (95% CI, 8.1 to 14.4 months); in metastatic patients, the median overall survival was 9.5 months (95% CI, 5.6 to 13.7 months, and in locally advanced patients, it was 15.7 months (95% CI, 8.9 to 43 months). The 1-year survival rate was 43% for the whole group (Fig 1). Six patients (including three patients with metastatic disease) are still alive, with a mean follow-up of +30 months (range, +26 to +33 months).

Safety

All treated patients (n = 46) were assessable for safety, and no treatment-related deaths occurred. Grade 3 to 4 toxicities are listed in Table 4. The most common toxicity was hematologic, with 52% of patients experiencing a grade 3 or 4 neutropenia in 22% of cycles. Grade 4 febrile neutropenia occurred in two patients (4%) without growth factors support. Overall, four patients received G-CSF for 12 cycles. The other grade 3 or 4 treatment-related hematologic toxicities were anemia and thrombocytopenia, which occurred in 18% and 6% of patients, respectively.

Nonhematologic toxicities of grade 3 to 4 occurred in less than 5% of cycles. Grades 3 and 4 vomiting was observed in 20% and 17% of patients, respectively, and grades 3 and 4 asthenia occurred in 20% and 2% of patients, respectively. Diarrhea led to hospitalization for four patients. Thirteen percent and 15% of patients experienced grades 2 and 3 peripheral neuropathy, respectively, leading to study discontinuation for seven patients (15%).

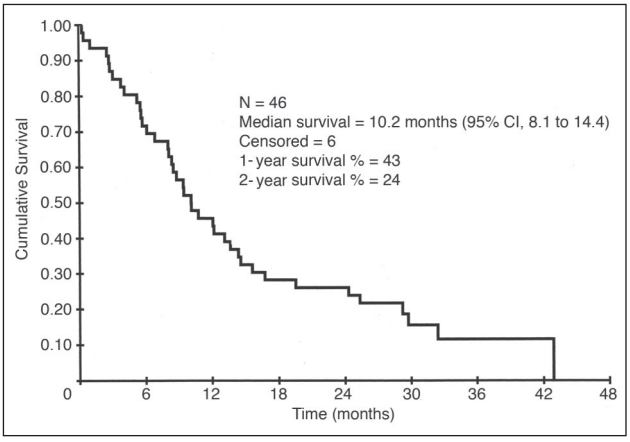

Fig 1. Overall survival in all treated patients.

Table 4. Main Grade 3 to 4 Toxicities Related to Study Treatment

Toxicity	Per Patient (N = 46)				Per Cycle (N = 356)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Hematologic toxicities								
Neutropenia	16	35	8	17	54	15	24	7
Febrile neutropenia	—	—	2	4	—	—	2	1
Anemia	5	11	3	7	7	2	3	1
Thrombocytopenia	2	4	1	2	2	1	1	< 0.5
Main nonhematologic toxicities								
Diarrhea	7	15	1	2	11	3	1	< 0.5
Nausea	9	20	—	—	9	3	—	—
Vomiting	8	17	—	—	9	3	—	—
Asthenia	9	20	1	2	16	4	1	< 0.5
Peripheral neuropathy	7	15	NA	NA	10	3	—	—
Alopecia*								
No.	9				NA			
%	20				NA			

*Grade 2.

QOL

Among all patients, 256 (65.8%) of a possible 389 EORTC QLQ-C30 forms were completed. For eight patients (17%), no baseline questionnaire was available. There was no difference between the overall population and the 38 patients who completed the baseline questionnaires regarding sex ratio, PS, median age, and disease stage. Two patients who had completed the baseline questionnaire failed to complete further forms. Patients with objective response and those with minor response (n = 5) were classified as responders (n = 14) for the QOL analysis and were compared to patients with stable (n = 12) or progressive disease (n = 12). Median scores at baseline and at the end of study treatment are listed in Table 5 together with the percentage of patients with 10 points in degradation or improvement of each scores.

Regarding the primary QOL end point, global QOL scores deteriorated in 18.8% of the patients, and 37.5% reported a moderate improvement (≥ 10 points). Of note, the global QOL score was improved by 25 points in responders, a major improvement according to the criteria of Osoba et al.[41] The scores of the secondary QOL objectives of fatigue, pain, and physical and emotional functioning improved by more of 10 points in 36%, 53%, 21%, and 36% of the patients, respectively. Changes in global QOL scores were associated with treatment response ($P = .003$). Global QOL scores at baseline were not predictive of treatment outcome ($P = .54$).

Table 5. Changes in QOL Scores From Baseline to the Last Known Values

Domains of EORTC QLQ-C30	Baseline Scores (n = 38)		End of Treatment Scores (n = 36)		Overall (n = 36)		MR + CR + PR (n = 13)	
	Median	Range	Median	Range	% of Patients With 10 Points Degradation	% of Patients With 10 Points Improvement	% of Patients With 10 Points Degradation	% of Patients With 10 Points Improvement
Functional scales*								
Global QOL	58.3	16.7-100	66.7	0-100	18.8	37.5	0	66.7
Physical	86.7	6.7-100	90	33-100	21.2	21.2	15.4	53.8
Role	66.7	0-100	83.3	0-100	31.3	40.6	23.1	69.2
Cognitive	100	33.3-100	83.3	50-100	30.3	27.3	30.8	38.5
Emotional	70.8	8.3-100	75.0	42-100	12.1	36.4	0	61.5
Social	66.7	0-100	100	0-100	21.2	48.5	7.7	61.5
Symptom scales†								
Fatigue	33.3	0-100	33.3	0-100	36.4	36.4	15.4	69.2
Nausea and vomiting	0.0	0-100	0.0	0-100	24.2	33.3	7.7	46.2
Pain	33.3	0-100	16.7	0-100	15.6	53.1	8.3	75.0
Single items†								
Dyspnea	33.3	0-100	0.0	0-66.7	9.1	33.3	0	61.5
Insomnia	33.3	0-100	33.3	0-100	18.2	36.4	7.7	69.2
Appetite loss	33.3	0-100	0.0	0-100	12.1	51.5	0	61.5
Constipation	33.3	0-100	0.0	0-100	6.1	51.5	7.7	61.5
Diarrhea	0.0	0-100	33.3	0-100	34.4	21.9	16.7	41.7

Abbreviations: QOL, quality of life; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; MR, minor response; CR, complete response; PR, partial response.
*High score = high level of functioning.
†High score = high level of symptoms.

Median scores of all functional scales improved during treatment, except cognitive functioning. Most symptoms such as pain, dyspnea, appetite loss, and constipation decreased under treatment except diarrhea. Fatigue and nausea were unchanged.

DISCUSSION

APA remains an incurable disease, and weekly gemcitabine has been widely adopted today as the standard of care in first-line chemotherapy for APA, with median survival limited to the range of 4.6 to 6.6 months in randomized studies.[7-10,12,14,15,42-45] Multivariate Cox regression analysis identified prognostic factors for survival, mainly PS, extent of disease (nonmetastatic *v* metastatic), albumin level, lactate dehydrogenase, alkaline phosphatases, age, tumor differentiation, and appetite loss.[7,43,44,46] Until now, no randomized trial has shown a significant QOL benefit or overall survival superiority for any gemcitabine-based combination over gemcitabine alone.[7-15,43] Therefore, better systemic therapies are warranted.

In this study, we offered Folfirinox for good PS patients (Eastern Cooperative Oncology Group PS of 0 and 1). Patients with Karnofsky PS less than 70 have a short median survival (eg, 2.4 months when treated with gemcitabine)[47] and were not eligible for this potentially toxic regimen. In this selected population, Folfirinox regimen seems promising and has a favorable tolerance profile. Despite a high rate of grade 3 to 4 neutropenia (52% of patients, 22% per cycle), only two cases of febrile neutropenia occurred. Hematologic toxicities resulted in 9% of cycles with dose reduction and 21% delayed cycles. These results may be improved with a larger use of G-CSF because only three patients received prophylactic G-CSF. The other toxicities were manageable, and no toxic deaths occurred.

Because of a frequent desmoplastic reaction in APA, tumor response assessment is difficult, especially in locally advanced disease. However, there was no major difference between the investigators and the ERRC conclusions. The encouraging response rate of 26% (CI 95%, 13% to 39%) with Folfirinox was similar in locally advanced disease (27.3%) and in metastatic disease (25.7%). In our study, all responses were confirmed by a second assessment and were independently reviewed. Two CRs, a rare event in APA, were observed (durations of 11 and 12 months). The overall response duration of 9.3 months (CI 95%, 8.2 to 13.6 months) is also encouraging. The overall tumor growth control was 61%, with a duration of 9.3 months (CI 95%, 7.8 to 11.7 months). Although second-line chemotherapy is often considered ineffective in APA, it was offered to 67% of patients, and one can not completely rule out some clinical impact resulting in an improved survival.

Patient QOL can be greatly reduced by side effects of chemotherapy or symptoms of APA, which include severe pain, depression, weight loss, loss of appetite, and fatigue. QOL was measured in our study with the EORTC QLQ-C30. As in all studies, the major problem with QOL assessment was the compliance, and eight questionnaires were lacking at baseline. However, the attrition rate was low, and at the end of treatment, data were available for all patients except two. All functional scales improved during treatment, except cognitive functioning. The greatest improvement in median scores was seen for role functioning, social functioning, and global QOL. Responders had the greatest improvement, with a median improvement of 25 points in global QOL, which is a major change according to Osoba criteria.[41] The median score of fatigue remained stable, and pain, dyspnea, insomnia, appetite loss, and constipation were improved. The only item that deteriorated during treatment was diarrhea.

Until now, few studies have demonstrated a QOL improvement with chemotherapy in APA. In 1996, Glimelius et al[5] reported on 53 patients randomly assigned to receive chemotherapy (FU and leucovorin with or without etoposide) plus BSC or BSC alone. Changes in EORTC QLQ-C30 were categorized by two assessors who were unaware of the patient group assignment. Eleven patients (38%) were considered to have a favorable QOL outcome in the chemotherapy group compared with three patients (13%) in the BSC group. However, the sample size was small, and the QOL evaluation was limited to the first 4 months. Most of the further studies showed a rapid degradation in QOL during chemotherapy, probably mostly because of tumor progression. In only one study, global QOL at 24 weeks was significantly superior to the pretreatment value with a FU-mitomycin combination.[46] The pain and dyspnea scores were also improved. Two studies have formally assessed QOL during gemcitabine treatment. Results are contradictory, with improvement of QOL in one study[8] and worsening of QOL at 4 and 8 weeks in another.[44]

Other trials have assessed irinotecan or oxaliplatin in APA. The combination of gemcitabine plus irinotecan is active in APA.[48] A randomized phase III study comparing gemcitabine alone to gemcitabine-irinotecan was recently published.[12] The confirmed response rate was significantly better in the two-drug regimen than with gemcitabine alone (16.1% *v* 4.4%, respectively; $P < .001$). However, there was no difference in PFS, overall survival, and QOL. The efficacy of oxaliplatin was tested in a three-arm randomized phase II study comparing oxaliplatin 130 mg/m^2, FU 1 g/m^2/d continuous infusion for 4 days, and the two drugs combined; the response rates were 0%, 0%, and 10% respectively. Tolerance was excellent, and the median survival of 9 months in the oxaliplatin-FU arm was encouraging.[28] Sixty-two patients were treated in a Groupe d'Etude et de Recherche Clinique en Oncologie et Radiothérapie (GERCOR) phase II study with a fixed dose-rate infusion of gemcitabine 1,000 mg/m^2 as a 10 mg/m^2/min infusion on day 1 and oxaliplatin 100 mg/m^2 on day 2 every 2 weeks (Gemox). The response rate was 30.6%.[49] Using 3-week Gemox schedule, the North Central Cancer Treatment Group[50] had a response rate of only 10.9%. The differences in these results suggest that the manner in which the drugs are administered influences the regimen's efficacy. An ongoing three-arm phase III study by the Eastern Cooperative Oncology Group will better clarify both the benefits of the fixed dose-rate infusion of gemcitabine and the added benefit of oxaliplatin. A randomized phase III study comparing the GERCOR's Gemox combination to standard weekly gemcitabine was recently presented.[11] Of 313 eligible patients, the response rate according the investigators was 26.8% for the Gemox combination versus 17.3% for gemcitabine alone ($P = .02$); PFS was 5.8 and 3.7 months, respectively ($P = .038$). However, no significant increase in survival was observed, and QOL was not measured.

In conclusion, the Folfirinox regimen seems promising for good PS patients. The objective response rate was 26%, including two CRs, and tumor control was achieved in 61% of patients. The median duration of response (9.3 months) and the median survival (10.2 months) are encouraging. Toxicity, which was mainly hematologic, was manageable, and an improvement in almost all the EORTC QLQ-C30 QOL domains was observed. This investigational combination is now tested in an ongoing phase II to III trial versus gemcitabine in patients with metastatic pancreatic cancer.

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Emmanuelle Magherini, Aventis; Aliette Hua, Aventis. Consultant/Advisory Role: Bernard Paillot, Aventis; Eric Francois, Aventis; Gael Deplanque, Aventis, Sanofi-Synthelabo. Stock Ownership: Emmanuelle Magherini, Aventis. Honoraria: Gael Deplanque, Aventis, Sanofi-Synthelabo. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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