Modulation of GemOx chemotherapy according to CIRS in elderly patients with advanced pancreatic cancer

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Abstract. The present study evaluated activity and toxicity of modulated doses of gemcitabine associated to oxaliplatin in patients with secondary CIRS and with locally advanced pancreatic adenocarcinoma (LAPC) and metastatic pancreatic adenocarcinoma (MPC). Since January 2006, untreated LAPC and MPC patients have been assessed with ADL, IADL, CIRS to modulate chemotherapy dosages according to co-morbidity stage. Patiens aged <75 years, co-morbidity stage primary/intermediate, or ≥75 years and co-morbidity stage primary, received gemcitabine 1,000 mg/m^2 as a 10 mg/m^2/min infusion on day 1 and oxaliplatin 70 mg/m^2 as a 2-h infusion on day 2 every 2 weeks. Patiens aged <75 years, co-morbidity stage secondary or ≥75 years and co-morbidity stage intermediate/secondary patients received gemcitabine 800 mg/m^2. Primary endpoint was the overall response rate (ORR). Secondary endpoints were disease control rate (DCR), PFS, OS and toxicity. Thirty-one patients were recruited: 26% (8/31) LAPC and 74% (23/31) MPC; median age 69 years. Co-morbidity stage primary/intermediate, 19; secondary, 12. Twenty-seven valuable patients: ORR 30% (CI±0.14); disease control rate 85% (CI±0.18). Median follow-up 13 months: median PFS and OS were 6 and 15 months, respectively. Valuable cycles 140. Grade 3/4 toxicity per patient: leukopenia, 18.5%; neutropenia, 55,5%; thrombocytopenia, 7.4%; SGOT/SGPT, 7.4%; gamma-GT, 7.4%; fever without neutropenia, 3.7%. Median received dose intensity: gemcitabine 400 mg/m^2/w; oxaliplatin 35 mg/m^2/w. Modulation of GemOx chemotherapy according, to CIRS stage in advanced pancreatic cancer confirms reported efficacy and tolerability.

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Introduction

Pancreatic cancer accounts for 3% of all new cases of tumor, with an incidence rate of 11.7% for all races from 2002 to 2006 and 42,470 estimated new cases in United States in 2009 (1-3). At the time of diagnosis, approximately half of the patients have metastatic disease, and the median survival does not exceed 6 months; whereas approximately one third of patients with locally advanced disease have median survival times ranging between 6 and 9 months (4).

Pancreatic cancer is the fourth leading cause of cancer death and median age of death is 73 years with an overall 5-years relative survival rate of 5.5% for men and women.

During the last 12 years, gemcitabine (Gem) has been considered the standard treatment for advanced pancreatic disease because of its superiority, as a single agent chemotherapy compared to 5-fluorouracil with an overall response rate (ORR) and progression-free survival (PFS) of 5.4% vs. 0% and 2 months vs. 1, respectively (5).

The Louvet phase II and III studies showed that the addition of oxaliplatin (I-OHP) to gemcitabine statistically improves ORR and clinical benefit, up to 26.8 and 38.2%, respectively, PFS, up to 5.8 months, compared with gemcitabine alone.

Other multiple cytotoxic (6-30) and anti-target (31,32) agents were used in association with gemcitabine but failed to show statistically relevant increase of activity and efficacy.

Recently, the addition of capecitabine to gemcitabine compared with gemcitabine alone (33) demonstrated an improvement in terms of ORR (19.1% vs. 12.4%, p=0.34) and PFS (5.3 vs. 3.8 months, p=0.04) with a trend toward improved OS (7.1 vs. 6.2 months, p=0.08).

In Western countries with increasing life expectancy, there is an increasing of the cancer incidence in the population >65 years particularly for pancreatic cancer. In fact, advanced pancreatic cancer patients show median age of 72 years. Approximately 68.4% are diagnosed at an age >65 years, 26.1% (young-elderly) at 65-74 years and 29.4% (old-elderly) at 75-84 years. Only 31.6% are diagnosed at <65 years.

Table I. Choice of schedule.

Age of patients	<75 years	≥75 years
Primary CIRS	Gemcitabine 1000 mg/m^2 g1-oxaliplatin 70 mg/m^2 g2 q14 (A-schedule)	Gemcitabine 1000 mg/m^2 g1-oxaliplatin 70 mg/m^2 g2 q14 (A-schedule)
Intermediate CIRS	Gemcitabine 1000 mg/m^2 g1-oxaliplatin 70 mg/m^2 g2 q14 (A-schedule)	Gemcitabine 800 mg/m^2 g1-oxaliplatin 70 mg/m^2 g2 q14 (B-schedule)
Secondary CIRS	Gemcitabine 800 mg/m^2 g1-oxaliplatin 70 mg/m^2 g2 q14 (B-schedule)	Gemcitabine 800 mg/m^2 g1-oxaliplatin 70 mg/m^2 g2 q14 (B-schedule)

Besides, they frequently show symptoms and metabolic dysfunction and/or comorbidities limiting the administration of combination chemotherapy at the projected DI; these reasons may justify the failure of all proposed associations to demonstrate overall survival advantage.

Very often these patients are characterized by co-morbidity, polipharmacology, altered nutritional status, absence of a proper care giver, impaired cognitive and poor adaptation of activities of life. Poor data are available in regard to the clinical management and therapeutic approach of pancreatic cancer patients according to young and/or elderly age and comorbidities (34-40).

Thus, we modulated GemOx in advanced pancreatic cancer patients according to age and CIRS to treat them using two schedules. The present study evaluated activity, efficacy and safety in the overall patients and in the two subgroups receiving the modulated GemOx.

Materials and methods

Patient eligibility. Patients were eligible for inclusion if they had histologically or cytologically confirmed diagnosis of measurable or assessable advanced and/or metastatic adenocarcinoma of the exocrine pancreas; age ≥18 years; World Health Organization (WHO) performance status (PS) ≤2; adequate hematological, renal and hepatic functions; patients previously treated with adjuvant chemo-radiotherapy were enrolled into the study but the treatment had to be completed at least 4 weeks before; life expectancy was more than 3 months for all patients.

Patients were ineligible due to pregnancy and/or lactation; myocardial infarction or angina pectoris within one year; uncontrolled severe diseases or active infections; cardiovascular disease (uncontrolled hypertension, uncontrolled arrhythmia, thromboembolic disease); suspected disseminated intravascular coagulation and biliary obstruction. Previous chemotherapy for metastatic disease was not allowed. All patients provided written and informed consent.

Study design. This was a preplanned double-arm clinical practice study, evaluating activity and tolerability of cytotoxic doublet gemcitabine and oxaliplatin administered according to two different schedules.

Patients were allocated to arm A or B according to Cumulative Illness Rating Scale (CIRS) (41): arm A included patients <75 years, co-morbidity stage primary and intermediate, or ≥75 years and co-morbidity stage primary; patients <75 years, co-morbidity stage secondary or ≥75 years and co-morbidity stage intermediate/secondary were allocated to arm B (Table I).

Schedule. Two different doses of gemcitabine were used in association with oxaliplatin: A-schedule, consisted of Gemcitabine (Gemzar®, Eli Lilly) 1,000 mg/m^2 day 1 and 15; oxaliplatin, l-OHP (Eloxatin®, Sanofi-Aventis), 70 mg/m^2 day 2 and 16; B-schedule, the same schedule, with a dose of gemcitabine of 800 mg/m^2. The treatment was repeated every two weeks and one cycle lasted 28 days.

Gemcitabine was administered over 100 min as intravenous infusion in 250 ml of NaCl 0.9%; OHP, over 2 h as an intravenous infusion in 250 ml of dextrose 5% (from 3 p.m. to 5:00 p.m.).

Patient evaluation. The first baseline assessment involved age and WHO performance status and then enrolled patients were processed with Activity Daily Living (ADL) (42), Instrumental Activity Daily Living (IADL) (43), Cumulative Illness Rating Scale (CIRS).

ADL allowed us to define patients: dependent, partially dependent, independent in their usual living activity.

IADL classified patients as: dependent and independent in their social and domestic life. Based on severity of co-morbidity, CIRS stratified patients in stable and instable category.

The combination of the three test results identified three stages: primary, independent ADL and IADL, absent or stable CIRS; intermediate, dependent ADL and/or IADL, stable CIRS; secondary, dependent ADL and/or IADL, instable CIRS.

Medical and family history, clinical symptoms, PS, weight, pain assessment (using visual analogue scale and analgesic consumption), physical examination and routine laboratory studies (blood cells count, serum creatinine and azotemia, bilirubin, AST, ALT, LDH, GGT, alkaline phosphatase, electrolytes, coagulation function) were performed in the prior week preceding treatment initiation and every two weeks

Table II. Distribution of treatment.

CIRS	A-schedule	B-schedule	Total
Primary/Intermediate	18	1	19
(%)	(95)	(5)	(100)
(%)	(100)	(8)	(61)
Secondary	-	12	12
(%)	(-)	(100)	(100)
(%)	(-)	(92)	(39)
Total	18	13	31
	(58)	(42)	(100)
	(100)	(100)	(100)

on-treatment. Tumor marker CA19.9 and electrocardiogram were tested in each cycle of treatment. An echocardiogram was required at baseline, and, at least, every 3 cycles of treatment thereafter for patients ≥65 years or young patients with high risk factor for cardiovascular disease. Blood count was evaluated every week thereafter on treatment.

Primary endpoint was ORR. Secondary endpoints were disease control rate (DCR), PFS, OS and toxicity. Complete responses, partial responses and stable disease were considered as DCR. PFS was calculated from the first day of treatment until evidence of clinical progression. OS was calculated from histological diagnosis until the day of death.

ORR was evaluated according to RECIST criteria (44). Clinical evaluation of response was made with TAC and/or RMN and was assessed every three months or earlier when clinically indicated. Patients were evaluated for toxicity every two weeks according to National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0). DLT (dose limiting toxicity) was defined as grade 3-4 non-haematological toxicity (mainly represented by diarrhea, mucositis, neurotoxicity, hand-foot syndrome, asthenia), grade 4 neutropenia, febrile neutropenia, grade 4 hematologic toxicity, or any toxicity that results in a >2 weeks delay of treatment.

Activity, efficacy and toxicity were also evaluated in the two subgroups of patients treated with modulated gemcitabine-doses according to CIRS. In A-schedule, gemcitabine dose reduction to 800 mg/m^2 was planned on the basis of non-neurologic DLT observed in the previous cycle. In B-schedule, gemcitabine dose was decreased by 10% after it was revealed a non-neurologic DLT. Oxaliplatin dose reduction was not planned related tolerability given (45,46). In case of laryngo-pharyngeal dysesthesia, OHP infusion was prolonged to 6 h and eventually stopped with other symptoms.

Results

Patient demographics. From January 2006 until January 2010, 31 consecutive unselected patients affected by LAPC and MPC were enrolled: median age, 69 years; 6 (19%) patients <65 years, 21 (68%) (young-elderly) patients ≥65 years <75, 4 (13%) (old-elderly) patients ≥75 years; male/female, 13/18; ECOG Performance Status 0/1/2, 10/16/5 pts. Stage of CIRS was: primary in 6 (19%) patients, intermediate in 13 (42%), secondary in 12 (39%). The only patient with intermediate CIRS in B-arm was 77 year-old (Table II). Metastatic disease in 23 (74%) patients, locally advanced disease in 8 (26%). Primary tumor: pancreatic head in 17 patients, pancreatic body in 11, pancreatic tail in 3. Median CA19.9 serum level was 1651 U/ml. Patients suffering from metastatic synchronous and metachronous disease were 20 (65%) and 3 (10%), respectively. Metastatic sites were: liver 15 patients (48%), peritoneaum 8 (26%), bone 5 (16%), lung 5 (16%), lymph nodes 4 (13%), pleura 2 (6%) (Table III).

Co-morbidity evaluation. Among 31 patients co-morbidity was classified according to CIRS (Fig. 2). Cardiac diseases in 7 patients (23%), median age 71 years, male/female 3/4: 2 patients (6%) with arrhythmia, 5 (16%) with heart disease, 4 (13%) with hypertensive heart disease and 1 (3%) patient with atherosclerotic heart disease. Hypertension 18 patients (58%), median age 71 years, male/female 8/10. Vascular pathology 5 patients (16%), median age 71 years, male/female 4/1: 1 (3%) with thrombocytopenia, 1 (3%) with monoclonal

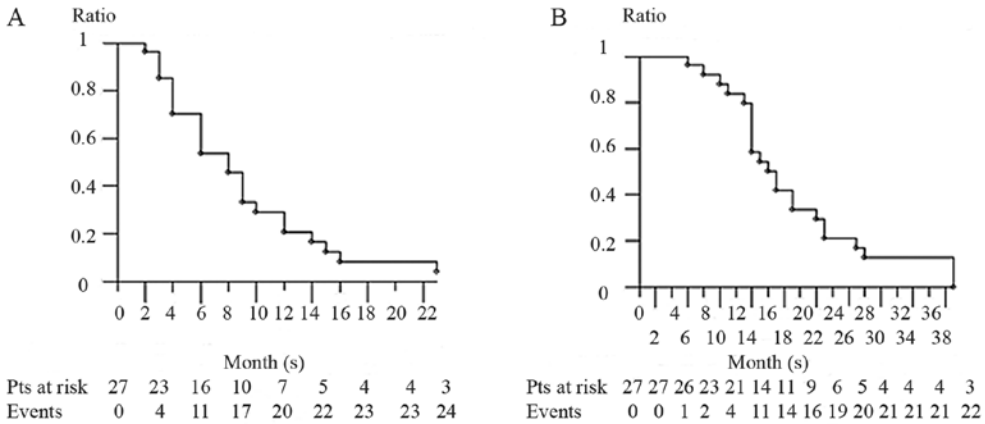

Figure 1. Progression-free and overall survival. (A) Progression-free survival (Kaplan-Meier method): 8 month(s) (2-29+). Median follow-up: 13 month(s), 24 events. (B) Overall survival (Kaplan-Meier method): 17 month(s) (6-39). Median follow-up: 13 month(s), 22 events. Pts, patients.

Table III. Patient clinocopathological characteristics.

	Total	A-GCT dose schedule	B-GCT dose schedule
Patients (No.)	31	18	13
Median age, years	69	66	71
Range, years	52-78	53-78	52-77
≥75 years, N (%)	4 (13)	1 (6)	3 (23)
≥65 and <75 years, N (%)	21 (68)	14 (78)	7 (54)
<65, N (%)	6 (19)	3 (16)	3 (23)
Sex, N (%)			
Male	13 (42)	6 (33)	7 (54)
Female	18 (58)	12 (67)	6 (46)
ECOG performance status, N (%)			
0	10 (32)	8 (44)	2 (15)
1	16 (52)	9 (50)	7 (54)
2	5 (16)	1 (6)	4 (31)
Status of CIRS, N (%)			
Primary	6 (19)	6 (33)	-
Intermediate	13 (42)	12 (67)	1 (8)
Secondary	12 (39)	-	12 (92)
Disease, N (%)			
Locally advanced	8 (26)	5 (28)	3 (23)
Metastatic	23 (74)	13 (72)	10 (77)
Primary tumor, N (%)			
Head	17 (55)	7 (39)	10 (77)
Body	11 (35)	9 (50)	2 (15)
Tail	3 (10)	2 (11)	1 (8)
Median CA19.9 serum level, U/ml, N (%)	1651	1031	2395
Next therapy, N (%)			
Second line	12 (39)	6 (33)	6 (46)
Third line	2 (6)	2 (11)	-
Metastatic sites, N (%)			
Liver	15 (48)	9 (50)	6 (46)
Peritonaeum	8 (26)	4 (22)	4 (31)
Bone	5 (16)	3 (17)	2 (15)
Lung	5 (16)	3 (17)	2 (15)
Lymph nodes	4 (13)	2 (11)	2 (15)
Pleura	2 (6)	-	2 (15)
No. of involved sites, N (%)			
1	9 (29)	6 (33)	3 (23)
≥2	14 (45)	7 (39)	7 (54)

gammopathy undefined syndrome, 1 (3%) with unspecified anemia, 1 (3%) with venous insufficiency legs. One female patient (3%), 65 years, had pulmonary disease, specifically chronic obstruptive pulmonary disease. One male patient (3%), 72 years, was deaf mute (ORL disease). Upper gastrointestinal disease's in 5 patients (16%), median age 70 years, male/female 1/4: 3 (10%) with gastritis, 1 (3%) with gastroesophageal reflux disease, 1 gastrectomized patient (3%). Low gastrointestinal disease in 3 patients (10%), median age 70 years, male/female 1/2: 2 (6%) with colonic diverticula, 1 (3%) with ulcerative colitis. Liver disease in 3 patients (10%), median age 70 years, male/female 2/1: 2 (6%) with liver failure, 1 (3%) with HCV-related hepatitis. Renal disease in 2 (6%) male patients, median age 63 years: 1 nephrectomized patient (3%); 1 (3%) with renal lithiasis, benign prostatic hypertrophy in 2 patients (6%), median age 75 years. Muscoloskeletal disease in 2 patients (6%), median age 73 years, male/female 1/1: 1 (3%) with arthrosis and 1 (3%) with lower limb amputation due to work accident. Chronic vascular cerebropatia in 3 (10%) patients, median age 71 years, male/female 2/1. Endocrine metabolic disease in 12 (39%) patients, median age 69 years,

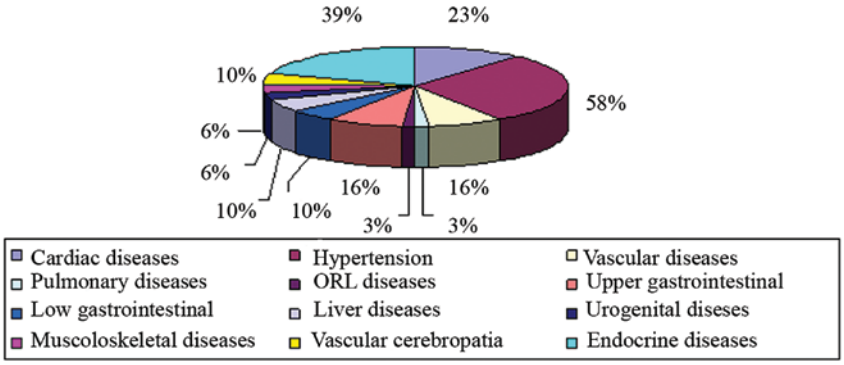

Figure 2. Co-morbidity evaluation.

Table IV. Efficacy.

	Total patients		A-schedule		B-schedule	
	N	%	N	%	N	%
No. of total patiens	31	100	18	100	13	100
No. of evaluable patients	27	87	15	83	12	92
Objective response	8	30	5	33.3	3	25
Partial response	8	30	5	33.3	3	25
Complete response	-	-	-	-	-	-
Stable disease	15	55	8	53.4	7	58
Progressive disease	4	15	2	13.3	2	17
Objective response rate	30% (α 0.05; CI ±0.14)		33.3% (α 0.05; CI ±0.25)		25% (α 0.05; CI ±0.25)	
Disease control rate	85% (α 0.05; CI ±0.13)		87% (α 0.05; CI ±0.18)		83% (α 0.05; CI ±0.22)	
Median PFS (month)	6 (2-29+)		8 (3-29+)		5 (2-16)	
Progression event	24		14		10	
Median OS (month)	15 (6-39)		15 (6-39)		16 (6-29+)	
Deaths	22		14		8	

male/female 6/6: 2 (6%) with hypothyroidism, 10 (32%) with diabetes.

We observed synchronous-co-morbidity in most patients: two co-morbidities in 8 patients (26%), three in 8 (26%), 4 in 5 (16%), 5 in 1 (3%). From 2 up to 5 co-morbidities were observed in 22 patients (71%).

Activity and efficacy. Among 31 enrolled patients, in the ITT and as treated analysis, 27 were evaluable: two patients did not received at least three cycles of treatment for biliary obstruction, chemotherapy was not administered for more than two weeks; one patient is on treatment and one patient was lost at follow-up. Altogether ORR was 30% (α 0.05; CI ±0.14). We observed 8 (30%) partial responses (PR), 15 (55%) stable disease (SD), 4 (15%) progressive disease (PD). DCR 85% (α 0.05; CI ±0.18) (Table IV). At a median follow-up of 13 months, median PFS was 6 months (2-29+): 24 events occurred and 3 patients are progression-free; median OS was 15 months (6-39): 22 deaths occurred and 5 patients are alive (Fig. 1).

Among 8 patients with locally advanced disease, 6 were evaluable: ORR was 33% (α 0.05; CI ±0.41). We had 2 PR (33%), 4 SD (67%). DCR 100%. After a median follow-up of 12 months, median PFS was 9 months (6-23): 5 events occurred and 1 patient is progression-free; median OS was 14 months (6-39): 5 events occurred and 1 patient is alive. In the subgroup of metastatic disease 21/23 patients were evaluable: ORR was 29% (α 0.05; CI ±0.19) with 6 PR (29%), 11 SD (52%), 4 PD (19%). DCR 81% (α 0.05; CI ±0.17). One patient (5%) had a pathological complete response (cRC): he had ductal pancreatic body adenocarcinoma with two liver metastases (0.8 and 1.2 cm, respectively) excised during laparoscopic surgery, treated with six months GemOx chemotherapy (A-schedule) and then with chemo-radiotherapy (45 Gy in 25 fractions over 5 weeks) with 5-fluorouracil 250 mg/m^2 in continuous infusion, then patient was processed to surgical excision of primary tumor (cRC). At a median follow-up of 13 months, median PFS was 6 months (2-29+): 19 events occurred and 2 patients are progression-free; median OS was 16 months (8-30+): 17 events occurred and 4 patients are alive.

ORR and DCR for the 15 valuable patients in A-schedule were 33.3% (CI ±0.25) and 87% (CI ±0.18), respectively. We observed 5 PR (33.3%), 8 SD (53.4%) and 2 PD (13.3%). Median PFS and OS were 8 (3-29+) and 15 (6-39) months, respectively.

Table V. Dose-intensity.

	pDI mg/m^2 (o kg)/w	Dose intensity/cycle mg/m^2 (o kg)/w	
		Median (Range)	Received DI (%)
A-schedule			
GEM	500	475 (286-500)	95
I-OHP	35	35 (17-35)	100
B-schedule			
GEM	400	400 (200-400)	100
I-OHP	35	35 (18-35)	100

pDI, projected dose-intensity; GEM, gemcitabine; OHP, oxaliplatin.

ORR and DCR for the 12 valuable patients in B-schedule were 25% (CI ±0.25) and 83% (CI ±0.22), respectively. Specifically we had 3 PR (25%), 7 SD (58%), 2 PD (17%). Median PFS and OS were 5 (2-16) and 16 (6-29+) months, respectively.

Dose-intensity. Median number of administered cycles in all 27 patients was 6 (standard deviation, SD, 2.04 cycle, range 3-10).

Median received dose intensities (rDI) per cycle were: Gem 400 (225-500) mg/m^2/w; I-OHP 35 (18-35) mg/m^2/w. Median received dose intensities (rDI) per patient were: Gem 400 (298-500) mg/m^2/w; I-OHP 35 (21-35) mg/m^2/w.

In A-schedule median rDI per cycle were: Gem 475 (286-500) mg/m^2/w, 95% of the pDI; I-OHP 35 (17-35) mg/m^2/w, 100% of pDI. Median rDI per patient were: Gem 425 (298-500) mg/m^2/w, 85% of pDI; I-OHP 35 (21-35) mg/m^2/w, 100% of pDI (Table V).

In B-schedule median rDI per cycle were: Gem 400 (200-400) mg/m^2/w, 100% of the pDI; I-OHP 35 (18-35) mg/m^2/w, 100% of pDI. Median rDI per patient were: Gem 400 (360-400) mg/m^2/w, 100% of pDI; I-OHP 35 (32-35) mg/m^2/w, 100% of pDI (Table V).

Patiens had a median cumulative I-OHP dose of 840 mg/m^2 (420-1400; SD 285; IC±108) and none had stopped I-OHP infusion for peripheral neuropathy.

Toxicity. One hundred and forty cycles were administered. In A-schedule 88 cycles (63%) were administered; cumulative G3-4 toxicities were: fever without neutropenia 1 patient (7%), elevation of SGOT/SGPT 2 patients (13%), GGT 2 (13%), leukopenia 4 (27%), neutropenia 10 (67%), thrombocytopenia 1 patient (7%). Two patients with elevation of SGOT/SGPT, 1 patient with neutropenia and the one patient with thrombocytopenia had DLT. Cumulative G2 toxicities were: nausea 1 patient (7%), vomiting 1 (7%), diarrhea 2 patients (13%), asthenia 5 (33%), dysgeusia 1 patient (7%), neurotoxicity 1 (7%), anorexia 1 (7%), fever 5 patients (33%), elevation of SGOT/SGPT 4 (27%), GGT 2 (13%), hypoalbuminemia 2 (13%), anemia 2 (2%), leukopenia 8 (53%), neutropenia 8 (53%), thrombocytopenia 6 (40%). Four cases of G4 neutropenia were observed, and no toxic deaths (Table VI).

In B-schedule 52 cycles (37%) were administered; cumulative G3-G4 toxicities were: leukopenia 1 patient (8%), neutropenia 5 patients (42%), thrombocytopenia 1 patient (8%). One patient with neutropenia G3 and the only patient with thrombocytopenia G3 had DLT. Cumulative G2 toxicities were: diarrhea 1 patient (8%), asthenia 5 patients (42%), anorexia 2 (17%), fever 1 patient (8%), elevation of SGOT/SGPT 1 (8%), GGT 1 (8%), anemia 1 (8%), leukopenia 3 patients (25%), neutropenia 4 (33%), thrombocytopenia 4 (33%). No cases of G4 neutropenia were observed, nor toxic deaths (Table VI).

Discussion

For many years gemcitabine monotherapy has been considered the standard treatment for advanced and metastatic pancreatic cancer because of an improvement of ORR and clinical benefit even if it does not increase OS vs. 5-fluorouracil. Furthermore, the extension from 30-min conventional gemcitabine time-infusion to 100 min (10 mg/m^2/min) was associated with an improved efficacy (47).

In regard to 5-fluorouracil, in a phase III study Berlin *et al* failed to demonstrate a statistically significant improvement of ORR (6.9 vs. 5.6%) and OS (6.7 vs. 5.4 months, p=0.09), but not for PFS (3.4 vs. 2.2 months, p=0.022), by adding 5-fluorouracil infusion to gemcitabine compared to gemcitabine alone. In another phase III study, combination chemotherapy containing gemcitabine and pemetrexed failed to demonstrate an increased efficacy in terms of ORR, PFS and OS.

Instead in a phase III trial, considering the association of cisplatin and gemcitabine, Heinemann *et al* demonstrated the statistically significant increase of PFS (5.3 vs. 3.1 months, p0.053), without statistically relevant differences in OS and ORR; recently in a randomized phase III trial, Colucci *et al* failed to demonstrate a statistically significant advantage in terms of PFS, OS and ORR, with the same cytotoxic association (28).

Moore *et al* showed an advantage in terms of OS and PFS but not of ORR by adding erlotinib to gemcitabine in first-line treatment of locally advanced (LAPC) and metastatic pancreatic cancer (MPC) (48). Also, the addition of bevacizumab to gemcitabine-erlotinib did not lead to a statistically significant improvement in OS in patients with metastatic pancreatic cancer. PFS, however, was significantly longer in the bevacizumab compared with placebo arm (49).

Recently Conroy *et al*, based on results of a phase II trial (50), with the preplanned interim analysis, demonstrated a statistically significant advantage in terms of ORR (31 vs. 9.4%, p=0.0001), PFS (6.4 vs. 3.3 months, p=0.0001) and OS (11.1 vs. 6.8 months, p=0.001) of the triple-association FOLFIRINOX compared with gemcitabine alone, in first-line MPC, in selected patients (PS 0-1, age 18-75, no evaluated co-morbidity). But despite the efficacy, this schedule is characterized of a no negligible toxicity profile. The grade 3/4 toxicities for patients (%) in arms FOLFIRINOX/gemcitabine were diarrhea 12.3/1.6, nausea 15.6/6.3, vomiting 17.2/6.3, fatigue 24/14.3, neutropenia 47.9/19.2 and febrile neutropenia 5.7/0. These toxicities do not allow use of such schedule in elderly patients with co-morbidity.

Table VI. Cumulative toxicities.

	(A) Gem (1000 mg/m^2) g1-Oxp (70 mg/m^2) g2 q14								(A) Gem (800 mg/m^2) g1-Oxp (70 mg/m^2) g2 q14							
	Patients				Cycles				Patients				Cycles			
Number	15				88				12				52			
Grade	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Nausea (%)	6 (40)	1 (7)	-	-	6 (7)	1 (1)	-	-	3 (25)	-	-	-	7 (13)	-	-	-
Vomiting (%)	3 (20)	1 (7)	-	-	3 (3)	1 (1)	-	-	2 (17)	-	-	-	2 (4)	-	-	-
Diarrhea (%)	7 (47)	2 (13)	-	-	11 (12)	3 (3)	-	-	4 (33)	1 (8)	-	-	8 (15)	1 (2)	-	-
Stomatitis (%)	3 (20)	-	-	-	4 (5)	-	-	-	-	-	-	-	-	-	-	-
Astenhia (%)	11 (73)	5 (33)	-	-	23 (6)	7 (8)	-	-	7 (58)	5 (42)	-	-	13 (25)	7 (13)	-	-
Peripheral sensory (%) neuropathy	12 (80)	1 (7)	-	-	34 (39)	1 (1)	-	-	8 (67)	-	-	-	16 (31)	-	-	-
Anorexia (%)	2 (13)	2 (13)	-	-	4 (5)	2 (2)	-	-	2 (17)	2 (17)	-	-	3 (6)	2 (4)	-	-
Alopecia (%)	2 (13)	-	-	-	2 (2)	-	-	-	-	-	-	-	-	-	-	-
Dysgeusia (%)	2 (13)	1 (7)	-	-	2 (2)	1 (1)	-	-	1 (8)	-	-	-	1 (2)	-	-	-
Fever (%)	2 (13)	5 (33)	1 (7)	-	6 (7)	8 (9)	1 (1)	-	1 (8)	1 (8)	-	-	1 (2)	2 (4)	-	-
Dermatology/skin (%)	1 (7)	-	-	-	1 (1)	-	-	-	-	-	-	-	-	-	-	-
Constipation (%)	3 (20)		-	-	7 (8)	-	-	-	1 (8)	-	-		1 (2)	-	-	-
SGPT/SGOT (%)	4 (27)	4 (27)	1[a] (7)	1[a] (7)	11 (3)	7 (8)	1[a] (1)	1[a] (1)	3 (25)	1 (8)	-		4 (8)	2 (4)	-	-
GGT (%)	3 (20)	2 (13)	2 (13)	-	5 (6)	2 (2)	4 (5)	-	-	1 (8)			-	1 (2)	-	-
Hypoalbulinemia (%)	-	2 (13)	-	-	-	2 (2)	-	-	1 (8)	-			1 (2)	-	-	-
Hypocaliemia (%)	-	-	-	-	-	-	-	-	2 (17)	-	-	-	3 (6)	-	-	-
Anemia (%)	5 (33)	2 (13)	-	-	8 (9)	2 (2)	-	-	3 (25)	1 (8)	-	-	4 (8)	2 (4)	-	-
Leukopenia (%)	7 (47)	8 (53)	3 (20)	1 (7)	8 (9)	15 (51)	3 (3)	2 (2)	2 (17)	3 (25)	1 (8)	-	3 (6)	9 (17)	1 (2)	-
Neutropenia (%)	6 (40)	8 (53)	6 (40)	4 (27)	6 (7)	13 (15)	15 (17)	4 (5)	2 (17)	4 (33)	4, 1[a] (33), (8)	-	2 4	4 (8)	9, 1[a] (17), (2)	-
Thrombocytopenia (%)	9 (60)	6 (40)	1[a] (7)	-	17 (19)	10 (11)	1[a] (1)	-	4 (33)	4 (33)	1[a] (8)	-	6 (12)	8 (15)	1[a] (2)	-

[a]DLT, dose toxicities limiting.

The improvement in terms of ORR (26.8 vs. 17.3%, p=0.04) and PFS (5.8 vs. 3.7 months, p=0.04) reached in the Louvet phase III trial, that compared OHP-gemcitabine association with gemcitabine alone, was the referral point for this clinical practice study (51).

Doublet gemcitabine and oxaliplatin did not show an improvement of OS, probably due to the poor balance between proper dose intensity (DI) of each drug and tolerability according to comorbidities of single patient independent of age. In fact in GemOx arm G3-4 neutropenia (20.4%), G3-4 thrombocytopenia (14%) and peripheral sensory neuropathy (19.1%) probably determined a lower administered D.I. of each drug and then efficacy.

The present study, proposes GemOx modulated chemotherapy in the first line treatment of consecutive, unselected LAPC and MPC patients, including 68% young-elderly and 13% old-elderly patients.

Majority of patients had hypertension under treatment (58%), endocrine-metabolic diseases (39%) including diabetes in 10 patients (32%), cardiac disease (23%), as expected for an elderly population; 22/31 patients (71%) had 2 or more co-morbidities and overall were treated with a doublet cytotoxic association. From literature data these elderly and suffering from pluri-co-morbidities patients are commonly treated with monochemotherapy or assigned to supportive care.

In order to administer a safer and equally effective regimen for advanced and metastatic pancreatic cancer in these patients as well, we designed a modulated schedule for young and elderly, fit and unfit patients. The target was administer, as soon as possible, a proper chemotherapy schedule to allow repeatable choices based on objective assessments.

Our regimen reached ORR 30% (CI±0.14) equivalent to Louvet phase II (52) and III study, 30.6 and 26.8%, respectively. We observed 30% (8/27) PR, 55% (15/27) SD, 17% (4/27) PD versus 30.6% (19/62) RP, 45% (28/62) SD, 24.4%(16/62) PD of the Louvet phase II study. DCR was 85% (CI±0.18) and was equivalent to the DCR (75%) of the Louvet phase II study, PFS (6 months in our GemOx-modulated schedule, 5.3 months in the Louvet phase II study and 5.8 months in the Louvet phase III study). In our experience OS was 15 months vs. 9.2 months of Louvet phase II trial and 9 months of the Louvet phase III study. The GemOx modulated schedule has the same efficacy of doublet cytotoxic standard.

A favorable toxicity profile was observed in all treated patients. In terms of NCI-CTC toxicities, the non-haematologic grade 3 or 4 observed were: 3.7% (1/27) fever without neutropenia; 7.4% (2/27) elevation of SGOT/SGPT; 7.4% (2/27) colesthasis. Grade 3 or 4 hematologic toxicities were: 18.5% (5/27) leukopenia; 18.5% (5/27) neutropenia (vs. 20.4% of the Louvet phase III trial) and the preventive use of growth-colony stimulating factors (G-CSF) were made in 3 patients without resistance; at last 7.4% (2/27) thrombocytopenia in comparison with 19.1% G3-4 thrombocytopenia in the Louvet phase III study (median time of platelet rescue in our experience was 11 days). There were no cases of febrile neutropenia and interruptions for cumulative neurologic toxicity. Overall DLT were observed in 5 patients (18.5%): 3 DLT (20%) in arm-A and 2 DLT (17%) in arm-B. The prevalent DLT was thrombocytopenia and it was equally distributed among A-schedule and B-schedule: 1 patient (7%) and 1 patient (8%), respectively. So, DLT was independent of co-morbidity stage. Limiting toxicity syndrome-single site (LTS-ss) in 1 patient (4%) in arm-B, limiting toxicity syndrome-multiple site (LTS-ms) characterized by DLT associated to other, at least G2, non-limiting toxicities in 4 patients (15%) whole in arm-A. There were not multiple DLT in the same patient.

This study confirms that LAPC and MPC patients are prevalently young and old-elderly and with pluripathology. The choice of modulation of this double-association using different schedules according to CIRS and age shows proof of efficacy with a favourable toxicity profile.

In fact B-GCT schedule's ORR (25%, CI±0.25) is acceptable if compared with the activity of a monochemotherapy or with any cytotoxic combination such as gemcitabine with 5-FU, UFT, epirubicin, docetaxel and irinotecan.

Based as they are on efficacy and safety these two schedules are recommended in LAPC and MPC patients with co-morbidities and routine employment of CIRS is advised in order to set a suitable and repetible choice.

Our study shows that planned modulation of GemOx chemotherapy according to CIRS age may guarantee equivalent activity and efficacy as well as manageable toxicity in advanced pancreatic cancer patients. Moreover, also old elderly patients, with consistent co-morbidities, can be safely treated using a combined chemotherapy. Present results may be used to better select other drugs to add if we consider the important results of the Prodige-Accord 11 phase II trial, that showed a statistically significant improvement of ORR, OS and PFS of the triplet association FOLFIRINOX compared with gemcitabine alone. But this triplet schedule has a value in patients with good performance status and no co-morbidities.

We can assert that the data confirm that pancreatic cancer is more common in the elderly population, group of patients heterogeneous due to co-morbidity (71% from 2 to 5). The metabolic dysfunction and/or comorbidity limit the DI and increase the toxicities. Despite the burden of disease (74% metastatic patients) co-morbidities and age has been maintained a good DI and tolerability, with no cases of death or high toxicity.

Gemox modulated schedule remains a valid choice to treat young and/or elderly patients with comorbidities, while triple-cytotoxic association, such us FOLFIRINOX, can be used in selected fit patients.

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