Safety of Cisplatin Combined with Continuous 5-FU *versus* Bolus 5-FU and Leucovorin, in Metastatic Gastrointestinal Cancer (FFCD 9404 Randomised Trial)

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Abstract. *Background: The objective of this phase III study was to compare the safety and efficacy of FLP (modulation of 5-FU (Fluorouracil) by folinic acid or leucovorin (LV) and cisplatin vs. FP (5-FU combined with Cisplatin) as a first line chemotherapy in advanced oesophageal, gastric and pancreatic cancer. Patients and Methods: 232 patients with measurable lesions were randomised to receive at the first cycle either FP (arm A: 5-FU 800 mg/m^2/d in continuous infusion 5 days and cisplatin 100 mg/m^2 on day 1 or 2), or FLP (arm B: LV, 100 mg/m^2/d in bolus 5 days, followed by 5-FU 350 mg/m^2/d in 1 h infusion 5 days and cisplatin 100 mg/m^2 on day 1 or 2). In case of no grade 3-4 haematological and diarrhoea toxicity, the dose of 5-FU was increased to 1,000 mg/m^2/d and 400 mg/m^2/d in the two arms respectively, for the subsequent cycles until disease progression. Results: The distribution of primary tumours was: 19 squamous cell carcinoma of the oesophagus, 19 oesophageal adenocarcinoma, 91 gastric and 97 pancreatic adenocarcinoma. Safety remained acceptable and comparable in the two arms except for the severe grade 3-4 mucositis, which was lower in arm B (4.5 vs. 16.4%, p<0.009). Efficacy in terms of tumour response and survival was similar in the two arms, showing an objective response rate (after external review) of 18.6% (95% confidence interval (CI) 11.4-25.8%) in arm A vs. 15% (95% CI 8.5-21.6%) in arm B, an overall median survival of 24 weeks in arm A vs. 24.7 in arm B (p=0.83) and a progression-free median survival of 12.4 weeks vs. 12.1 in arms A and B, respectively (p=0.91). Conclusion: The FLP regimen is substantially equivalent to FP in terms of safety and quality of life, as well as for antitumour efficacy in these carcinomas; the only slight advantage of FLP in this study concerns mucositis. Based on these results, FLP could be used as an alternative to FP when appropriate.*

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Oesophageal, gastric and pancreatic cancers remain frequent digestive carcinomas and are among the main causes of cancer death worldwide. At the metastatic stage, the prognosis is very poor in most studies. In term of response rate, the situation seems better in oesophageal carcinoma than in pancreatic cancer. Previous studies showed that the response rate is often around 50% in phase II studies (1-3) for the former, whereas the best response rates are no more than 10 to 20% for the latter. The combination of 5-fluorouracil (5-FU) in continuous infusion with cisplatin (FP) in both metastatic and locally advanced cases, sometimes with external irradiation, is widely used in oesophageal and gastric locations and was common for pancreatic cancer before the advent of gemcitabine. The synergistic activity of this combination has been demonstrated in both experimental models (4) and clinical studies (5). In metastatic gastric adenocarcinoma, the FP regimen has been well documented in three large phase II trials (6-8) and yielded overall response rates of 41%, 43% and 43%, with median survival times of 10.6, 9 and 7 months, respectively. In advanced pancreatic carcinoma, the same FP regimen has been explored in a monocentric phase II study. The response rate was 26.5% with a median survival of 7 months (9). At the time of commencing our study, this FP schedule was evaluated in two phase III trials, one in advanced gastric cancer and another in advanced pancreatic cancer (10, 11) .

The modulation of 5-FU with folinic acid has also been widely documented in various gastro-intestinal clinical studies (12, 13); moreover, two studies have tested, with encouraging results, the combination of leucovorin, 5-FU and cisplatin in head and neck cancers (14, 15). We previously described the results of the association of leucovorin and 5-FU (Mayo Clinic regimen) combined with cisplatin (FLP) in 27 evaluable patients with metastatic gastric cancer; this FLP regimen obtained a response rate of 51.8% (CI 95%, 33-70.6%) and a median survival of 11 months with a very low overall toxicity (Ychou M, 1996) (16) using leucovorin 200 mg/m^2/d (as a short infusion of 15 min) followed by 5-FU 400 mg/m^2/d for 5 days (as a 1 h infusion) with cisplatin 100 mg/m^2 on day 2. These results seemed very equivalent in terms of efficacy to those reported above with the FP regimen using 5-FU 800 to 1,000 mg/m^2/d for 5 days with cisplatin 100 mg/m^2/d on day 2 in the same metastatic gastric cancer patients (6-8), with a better tolerance profile.

Based on this background, the Federation Francophone de Cancérologie Digestive (FFCD) conducted a randomised phase III trial to compare the safety (primary objective), clinical efficacy and quality of life (secondary objectives) of FLP *vs.* FP, as a first line chemotherapy in patients with metastatic oesophageal, gastric and pancreatic carcinoma – three cancers tending to show a positive response to these molecules.

Patients and Methods

Patient selection. The eligibility criteria were as follows: histologically proven carcinoma of the oesophagus, the stomach or the pancreas, with measurable metastatic disease (≥15 mm) and without indication of radiotherapy and/or surgery; no prior chemotherapy for metastatic disease and, in case of adjuvant chemotherapy, no regimen containing cisplatin; age ≤75 years and World Health Organization (WHO) performance status <2; adequate baseline organ function, defined as neutrophile count ≥1,500/mm^3, platelet count ≥100,000/mm^3 and creatinine level <1.25 times the normal level; in cases where the patient was older than 70 years and/or the creatinine level was between 1 and 1.25 times the normal limit, creatinine clearance had to be more than 60 ml/mm; no severe uncontrolled co-morbidities and no brain metastases. Written informed consent approved by the local Ethical Committee was given by all the participants before they entered the study.

Stratification and randomisation. Patients were stratified according to institution, performance status (WHO 0 *versus* 1), type of primary tumour (oesophageal adenocarcinoma, *versus* oesophageal squamous cell carcinoma, *versus* gastric adenocarcinoma, *versus* pancreatic adenocarcinoma) and prior adjuvant chemotherapy. They were then randomly assigned to receive either an FP (arm A) or an FLP regimen (arm B) by the FFCD data centre Dijon, France, using the minimization technique.

Treatment plan. i) Treatment A: The FP regimen consisted of 5-FU at a dose of 800 mg/m^2/d in continuous infusion for 5 consecutive days and cisplatin at 100 mg/m^2 in a 1- h perfusion, given on day 1 or day 2.

ii Treatment B: The FLP regimen consisted of leucovorin at a dose of 100 mg/m^2/d in bolus for 5 consecutive days, followed by 5-FU at 350 mg/m^2/d in a 1-h infusion from day 1 to day 5 and cisplatin at 100 mg/m^2 given on day 1 or day 2.

The cycles were repeated every 28 days for each treatment. In cases with no grade 3-4 (WHO grading) haematological and diarrhoea toxicity at the first cycle, the dose of 5-FU was increased for the following cycles to 1,000 mg/m^2/d in arm A and 400 mg/m^2 in arm B. Treatment was continued until the disease progression in all patients and doses were adapted to the toxicity, a reduction of 25% was planned in case of haematological and/or digestive toxicity greater or equal to grade 3 during the interval between two cycles. Cycles were delayed until toxicity levels normalized. In the FLP arm, cisplatin could be stopped if renal, neurological or otological toxicity precluded further administration. The protocol treatment was stopped for tumour progression, grade 4 life-threatening toxicity or at the patient's request.

Pretreatment evaluation, follow-up and response evaluation. Baseline evaluation included a complete medical history and physical examination, standard biological tests, ECG, chest X-ray and computed tomographic (CT) scan of the measurable metastatic lesions. The patients were monitored before each cycle of chemotherapy, including assessment of clinical toxicities, blood cell count, serum chemistry, physical examinations and quality of life (QOL) assessment, according to Spitzer's index (1981). Hospitalisation durations were noted during and after the treatment. Between the first and the second cycle, blood cell count was performed every week, so as to increase the dose of 5-FU at the second cycle. Toxicities were evaluated and graded according to WHO criteria. Tumour response was assessed *via* a CT scan every two cycles of chemotherapy (every two months) in both arms and at the end of the treatment. After completion of the treatment, the patients with tumour response or stable disease were evaluated every two months until documented disease progression. WHO criteria were used to define the response and the response duration. CT scans were performed four weeks later to confirm the response. The CT scans of patients who achieved an objective response were centrally reviewed by an external panel of radiologists.

Statistical considerations. The aim of this study was to detect a difference of at least 15% in grade 3-4 toxicity (better tolerance expected in the FLP group), while observing a difference of less than 15% in the objective response rate (ORR) between the two regimens. The study was designed so as to require 116 patients per arm to provide at least 80% power in a one-sided test (with an α risk of 5%). After one year of recruitment, an independent committee was able to stop the trial in case of toxicity being too severe. The Mantel-Haenszel test was used to compare toxicity and responses between arms, using stratification on tumour location. Progression-free survival (PFS) and overall survival (OS) were calculated, using the Kaplan-Meier method, from the date of inclusion to progression (relapse, second cancer or cancer death) and death from any cause, respectively. The log-rank test was used to identify the prognostic factors and the Cox proportional hazard model was used for all multivariate analyses. All analyses were based on the intent-to-treat principle.

Table I. *Patient characteristics.*

	Arm A (FP)		Arm B (FLP)		
	n	(%)	n	(%)	*p*
Total	113	(100)	113	(100)	
Gender					
male	90	(79.6)	83	(73.5)	0.27
female	23	(20.4)	30	(26.5)	
Age (Years)					
mean (SE)	59.8 (0.9)		60.6 (0.9)		0.51
median (SE)	61.0 (0.9)		62.0 (1.1)		
range	38-75		41-76		
Prior adjuvant chemotherapy					
no	111	(98.2)	111	(98.2)	1.00
yes	2	(1.8)	2	(1.8)	
WHO performance status					
0	32	(28.3)	34	(30.1)	0.57
1	81	(71.7)	78	(69.0)	
2	0	(0.0)	1	(0.9)	
Primary tumour					
oesophageal adenocarcinoma	10	(8.8)	9	(8.0)	0.99
oesophageal SCC*	9	(8.0)	10	(8.8)	
gastric carcinoma	45	(39.8)	46	(40.7)	
pancreatic carcinoma	49	(43.4)	48	(42.5)	
Site of metastases					
liver	89	(78.8)	90	(79.6)	0.87
adenopathy	62	(54.9)	50	(44.2)	0.11
lung	24	(21.2)	13	(11.5)	0.05
peritoneal	12	(10.6)	15	(13.3)	0.54
other	23	(20.3)	16	(14.2)	0.81
Number of sites of metastases					
1	47	(41.6)	54	(47.8)	0.28
2 and >2	66	(58.4)	59	(52.2)	
Chronology of metastases					
synchronous	84	(74.3)	90	(79.6)	0.34
metachronous	29	(25.7)	23	(20.4)	
Size of institution **					
large	55	48.7	54	47.8	0.95
medium	32	28.3	31	27.4	
small	26	23.0	28	24.8	

*SCC: squamous cell carcinoma.
**Size of institution: large, ≥16 inclusions; medium, 7-15 inclusions; small, ≤6 inclusions.
FP: 5-fluorouracil and cisplatin; FLP: 5-fluorouracil, leucovorin and cisplatin.

Results

From April 1995 to April 1998, 232 patients with metastatic oesophageal, gastric or pancreatic carcinoma from 28 institutions (classified into three classes according to their size) were randomised. Six patients were ineligible (3%), four because of incorrect histology, one was not metastatic (liver angioma) and one had previously been treated with cisplatin.

The patient characteristics are listed in Table I. The two arms (113 patients per arm) were well balanced for the main characteristics: age, gender, prior adjuvant chemotherapy, performance status, location of primary tumour, number of metastatic sites and chronology of metastases. The repartition of primary tumour was as follows: 19 squamous cell carcinoma of the oesophagus, 19 oesophageal adenocarcinoma, 91 gastric and 97 pancreatic adenocarcinoma. Most of the patients (98%) had never received prior adjuvant chemotherapy.

Toxicity and dose-intensity. There were ten protocol violations: four patients received FP treatment in place of FLP, one patient (allocated in arm B) started the FP regimen and then continued with the FLP regimen and five

Table II. *Worst toxicities WHO grade 3-4 by patient according to the arm.*

Toxicity	Arm A (FP) (n=111 patients)		Arm B (FLP) (n=112 patients)		
	grade 3 (%)	grade 4 (%)	grade 3 (%)	grade 4 (%)	*P*
Leukopenia	10.8	2.7	12.5	3.6	0.67
Neutropenia	19.8	15.3	18.8	14.3	0.93
Thrombocytopenia	6.3	0.9	6.3	3.6	0.59
Anemia	11.7	3.6	21.4	2.7	0.13
Infection	3.6	0.9	5.4	1.8	0.56
Mucositis	12.6	3.6	3.6	0.9	0.009
Nausea/vomiting	22.5	2.7	30.4	2.7	0.26
Diarrhoea	7.2	0.9	8.9	2.7	0.48
Renal	0.9	0.0	0.0	0.0	0.99
Cardiac	0.9	0.0	2.7	0.0	0.61
Neurotoxicity	4.5	2.7	3.6	4.5	0.99
Alopecia	1.8	0.0	0.0	0.0	0.48
Ototoxicity	1.8	0.0	0.9	0.0	0.99
Maximum toxicity	45.0	33.3	37.5	32.1	0.17

Mantel-Haenszel test comparing grade 3-4 toxicities between arms with stratification on the primary tumour location.
FP: 5-fluorouracil and cisplatin; FLP: 5-fluorouracil, leucovorin and cisplatin.

patients were treated with additional radiotherapy (a tongue cancer, discovered 10 days after the inclusion, received radiotherapy). One ineligible patient (receiving the FLP regimen) was included by mistake despite having a poor WHO performance status (2). Two hundred and twenty-three patients were assessable for treatment description and toxicity. The median number of cycles before progression was 3 (SE=0.3) in arm A (range 1-12) and 3 (SE=0.2) in arm B (range 1-11); a total of 387 and 412 cycles were administered in arm A and B, respectively.

Toxicities were assessed for the first cycle and then for the whole range of cycles before progression; overall grade 3-4 toxic events are listed in Table II. Overall, 78.4% and 69.6% of the patients treated by the FP and FLP regimens, respectively, experienced WHO grade 3-4 toxic reactions ($p=0.17$). Haematological toxicity was very similar in the two groups. The major toxicity was neutropenia (FP=35.1% and FLP=33.0%). Although severe anaemia was more marked in arm B (24.1% *vs.* 15.3%), there was no significant difference between the two groups. The occurrence of nausea/vomiting was common with the use of high dose cisplatin, but was not statistically different between the two groups (arm A=25.2%, arm B=33.0%). The only significantly different toxicity observed between the two arms was mucositis, with 16.2% of the patients with grade 3-4 in arm A *versus* 4.5% in arm B ($p=0,009$). In spite of the use of cisplatin, nephrotoxicity and hearing loss were very mild, regardless of arm, and serious ototoxicity showed minor differences (not statistically significant) between the two arms (0.9% in arm B *vs.* 1.8% in arm A).

The toxicity profile was assessed according to the type of primary tumour. Compared with the other sites (oesophageal adenocarcinoma, squamous cell carcinoma or pancreatic adenocarcinoma), patients with gastric cancer developed the greatest grade 3-4 toxicities (81.4% *vs.* 57.9%, 72.2% and 70.5%, respectively $p=0.04$). Severe haematological toxicity (60.4% with 53.8% neutropenia) was very high in this location, compared with the other sites (31.6% and 26.3% in oesophageal adenocarcinoma, 33.3% and 11.1% in squamous cell carcinoma and 36.8% and 21.1% in pancreatic location, respectively, $p=0.0003$ and $p=0.0001$). Severe digestive toxicity occurred for 41.1% of the patients with pancreatic cancers, 21.1% of those with oesophageal adenocarcinoma, 22.2% with squamous cell carcinoma and 34.1% with gastric cancer ($p=0.10$).

These adverse effects were responsible for treatment interruptions in 11.5% of the cycles in arm A and 15.9% of the cycles in arm B. The occurrence of treatment interruption due to toxicity was very similar in the three sites (10.5%, 11.1% and 11.5% of cycles in oesophageal adenocarcinoma, squamous cell carcinomas and pancreatic cancer, respectively); patients with gastric cancer stopped their chemotherapy because of toxicity in 17.6% of cycles.

There were six toxic deaths: two in arm A and four in arm B. Two were due to neutropenic sepsis (arm B), two due to renal failure (one in arm A and one in arm B), one due to severe diarrhoea (arm B) and one due to ischemic attack (arm A, in a patient with predisposing factors). Administration delays were necessary in 22.5% of the cycles (arm A) and 25% of the cycles (arm B). The duration of the delay was similar in the two arms: ≤3 days in 9.6% of the cycles in arm A *vs.* 10.1% in arm B, 4-7 days in 9.0% of the cycles in arm A *vs.* 11.2% in arm B, greater or equal to 15 days in 1.6% and 1.2% of the cycles in arms A and B, respectively. Delays ≥15 days were only reported in patients with oesophageal adenocarcinoma and gastric cancer (3.9% and 3.1% of the cycles, respectively). The median doses of 5-FU and cisplatin received before progression were 831 and 95.7 mg/m^2/d, respectively in arm A representing a dose intensity of 89% and 95.7%, respectively, and 361.5 and 96.8 mg/m^2/d in the arm B, *i.e.,* a dose intensity of 94.3% and 96.8%, respectively.

Response rate. The overall responses to treatment for all 226 eligible patients (after expert review) are presented in Table III. The objective response rate, initially assessed by investigators, was identical in the two groups (20.4%). It remained similar after external review at 18.6% (95% CI 11.4-25.8%) in arm A, which was not significantly different from 15% (95% CI 8.5-21.6%) in arm B ($p=0.59$). The objective responses observed in patients were 7/19 (36.8%) with oesophageal adenocarcinoma, 4/19 (21%) with

Table III. *Overall objective responses rates (after expert review) according to the arm.*

Response	Arm A (FP) (n=113)		Arm B (FLP) (n=113)	
	No. of patients	%	No. of patients	%
Complete response	2	1.8	2	1.8
Partial response	19	16.8	15	13.3
Overall response	21	18.6	17	15.0
5% CI		[11.4-25.8]		[8.5-21.6]
Stable disease	29	25.7	28	24.8
Progressive disease	63	55.8	68	60.2

FP: 5-fluorouracil and cisplatin; FLP: 5-fluorouracil, leucovorin and cisplatin. 95% CI: 95% confidence interval

Table IV. *Survival data: Multivariate analysis.*

Variable	Relative risk of death	95% CI	*P*
Chemotherapy			
FP	1		0.28
FLP	1.17	0.88 – 1.54	
Primary tumour			
Gastric carcinoma	1		0.0002
Oesophageal adenocarcinoma	0.97	0.55 – 1.68	
Oesophageal SCC	1.67	0.98 – 2.83	
Pancreatic carcinoma	2.07	1.46 – 2.95	
Age			
<55 years	1		0.045
55-64 years	1.35	0.94 - 1.93	
>64 years	1.56	1.09 - 2.24	
WHO Performance status			
0	1		0.072
1-2	1.32	0.97 – 1.80	

SCC: squamous cell.
FP: 5-fluorouracil and cisplatin; FLP: 5-fluorouracil, leucovorin and cisplatin.
95% CI: 95% confidence interval.

oesophageal squamous cell carcinoma, 18/91 (19.8%) with gastric cancer and 9/97 (9.3%) with pancreatic cancer. The median duration of objective response was 23.9 weeks (SE=9.3 weeks) in arm A, which did not significantly differ from 24 weeks in arm B (SE=4.3 weeks, $p=0.51$). Median duration of response was similar ($p=0.22$) in the different sites of primary tumour: 27.7 weeks (SE=32.3 weeks) in oesophageal adenocarcinoma, 16.4 weeks (SE=11.5 weeks) in oesophageal squamous cell carcinoma, 24.0 weeks (SE=6.2 weeks) in gastric cancer and 22.8 weeks (SE=6.2 weeks) in pancreatic carcinoma.

Survival. Median overall survivals were not statistically different ($p=0.83$) at 24 weeks (SE=3.6) with FP and 24.7 weeks (SE=3.6) with FLP and. The one- and two-year survival rates were 21.5% (SE=3.9%) and 6.7% (SE=2.5%) respectively in arm A and 17.3% (SE=3.6%) and 2.8% (SE=1.9%) in the arm B. Considering the survival according to the location of the primary tumour, median overall survival was worst for pancreatic carcinoma (16.6 weeks, SE=2.1) than for oesophageal adenocarcinoma (31.3 weeks, SE=1.9), oesophageal squamous cell carcinoma (20.6 weeks, SE=1.1) and gastric cancer (39.7 weeks, SE=4.1).

The only statistically significant predictors of survival in univariate analysis were tumour location ($p<0.0001$) and performance status ($p=0.0013$). The number of metastatic sites was not a statistically significant factor, but there was a trend towards better survival when the disease was not very extensive ($p=0.062$). Survival in the treatment groups was compared after adjustment for these prognostic factors; the FLP regimen was not superior to the FP regimen in terms of survival ($p=0.28$) and the main factors which correlated with poor survival were the location of primary tumour in the pancreas ($p=0.0002$) and the age of the patient ($p=0.045$) (Table IV). Considering the median progression-free survival, the two regimens did not differ significantly (12.4 (SE=2.6) and 12.1 (SE=2.6) weeks with FP and FLP, respectively $p=0.91$). The one- and two-year survival rates were 9.4% (SE=2.8%) and 3.5% (SE=1.8%), respectively, in the FP arm and 5.3% (SE=2.1%) and 1.2% (SE=1.1%) in the FLP arm. As observed above, the progression-free survival was worst ($p=0.002$) for the pancreatic carcinoma, with a median survival time of 8.6 weeks (SE=4.2), than for the other locations (16 weeks (SE=4.3) for oesophageal adenocarcinoma, 13.4 weeks (SE=3.4) for oesophageal squamous cell carcinoma and 20 weeks (SE 3.6) for gastric cancer).

QOL was fairly well assessed until the sixth cycle (48 weeks) as questionnaire filling rates during the first six cycles were: 97.9%, 100%, 86.7%, 90.0%, 80.9% and 78.4%, respectively. During this period, there was no difference in Spitzer's scores between the two arms. From the seventh cycle, global QOL data were available for only 34.3% of the patients; therefore, they could not be analysed due to insufficient numbers.

The mean duration of hospital stay (during or after treatment) was not statistically different between the two arms: 38.3 days (SE=2.8) in arm A compared to 35.2 days (SE=0.6) in arm B, ($p=0.24$). When converted to days per month of life, the mean duration remained similar: 8.1 days (SE=0.7) for arm A and 7.4 days (SE=0.6) for arm B, ($p=0.42$). The total duration of hospital stay was shorter in pancreas carcinoma (29.8 days, SE=2.3) than in oesophageal adenocarcinoma (42.5 days, SE=7.5), oesophageal squamous cell carcinoma (36.2 days, SE=5.0) and gastric cancer (43.0

days, SE=3.1), but these differences were not observed when the duration of hospital stay was converted to days per month of life (7.3 days (SE=1.6) in oesophageal adenocarcinoma, 7.5 days (SE=1.5) in oesophageal squamous cell carcinoma, 7.3 days (SE=0.7) in gastric cancer and 8.3 days (SE=0.7) in pancreatic carcinoma).

Discussion

The primary objective of this phase III randomised study was to compare the tolerance between FLP and FP regimen in metastatic oesophageal, gastric and pancreatic carcinoma. The overall safety of these chemotherapies is very similar to most previous studies; grade 3-4 neutropenia and digestive toxicity occurred in approximately 30% and 20% of patients with gastric and pancreatic cancers, respectively (7, 9-11, 17). Maximum severe toxicity was very similar in the two arms. Only mild and particularly severe mucositis was statistically lower with the FLP regimen; this could be explained by the duration of the injection (1-h infusion instead of 120 h) combined with the lower dose of 5-FU (350 to 400 mg/m^2) in this arm. Similar observations had already been made by Ychou *et al.* (16) when using the same FLP regimen (with 1-h injection) showing no grade 3-4 mucositis in metastatic gastric cancer. Other worst toxicities, particularly neutropenia and digestive toxicities, are in the range reported by Vanhoefer *et al.* with an FUP regimen in gastric cancer (35% and 32%, respectively) (10). Gastric cancer cases were associated with the highest toxicity, which is a common observation.

Regarding the efficacy in terms of response, survival, QOL and hospital stays (which represent secondary objectives), no significant differences were found between the FP and FLP regimens. Our study confirms the activity of the combination of cisplatin/5-FU in the oesophageal adenocarcinoma location, in terms of response rate (37%), which is slightly better than the 33% observed in Ilson *et al.* phase II study (3). This efficacy, albeit real, is less significant in metastatic squamous cell oesophageal cancer (18). However, the number of patients with oesophageal cancer was too small to draw any valid conclusions.

Concerning the gastric location, the efficacy in terms of response rate observed in this trial (19.8%) is lower than those reported in previous phase II non-randomised studies using the same regimens; these showed response rates ranging from 41% to 52% (6-8, 16) . This could be due to a more selected population included in those phase II non-randomised trials. By contrast, the response rate reported in our trial concerns a non-selected population from a great number of centres (including non-specialised ones). However, this response rate is far from the one reported by Kim in a phase III trial (51%) (5) (unconfirmed by external review) but equivalent to that of 20% recently reported by Vanhoefer *et al.* (10) using FUP compared with FAMTX and ELF regimens. Recently, a slightly better response rate (27%) was obtained by Bouché *et al.* (19) in this condition with a combination LV5FU2-cisplatinum. In terms of survival, the overall median survival of 40 weeks in our trial is in the same range as that obtained by previous studies (9-11 months) and is better than the 7.2 months reported by Vanhoefer *et al.*

As for pancreatic location, the efficacy of FP or/and FLP (with an overall response rate of 9.3% and a median overall survival of 116 days) is rather disappointing, but similar to that reported in a trial conducted by the French Anticancer Centre (11), testing continuous 5-FU (1000 mg/m^2/day for 5 days) plus cisplatin (100 mg/m^2) (FUP) one day *vs.* 5-FU (500 mg/m^2/day for 5 days) (FU). This study showed a slight advantage for the FUP protocol compared with FU, with a response rate of 12% and 112 days of median survival. In this location, gemcitabine is now widely used, but has never been compared to a combination of 5-FU CDDP in a randomised trial, even if tolerance to gemcitabine was shown to be more favourable in two reports (20, 21).

The QOL data showed no differences between the study arms during the first six cycles; this is consistent with the similar duration of hospital stay reported in the two arms.

In conclusion, the FLP regimen was substantially equivalent to FP, as regards safety and QOL, as well as for antitumour efficacy in advanced gastric, pancreatic and oesophageal cancers; the only slight advantage of FLP in this study concerns mucositis. Based on these results, FLP could at most be, an alternative to FP when appropriate. However, recent data in gastro-intestinal cancer show that oral administration of 5-FU in combination schedules would replace intravenous administration of 5-FU in future trials.

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