Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301)

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ABSTRACT

Purpose Gemcitabine is the standard chemotherapy for patients with metastatic pancreatic adenocarcinoma. Although the 5-fluorouracil (5FU), folinic acid and cisplatin combination (LV5FU2-CDDP) is an option, the optimal order of the regimens must be determined. The first strategic phase III trial comparing LV5FU2-CDDP followed by gemcitabine versus gemcitabine followed by LV5FU2-CDDP was conducted.

Methods Patients with metastatic pancreatic adenocarcinoma, performance status (PS) 0–2, without prior chemotherapy were randomly assigned (1:1) to receive either LV5FU2-CDDP followed by gemcitabine at disease progression or toxicity (Arm A), or the opposite sequence (Arm B). 202 patients had to be included and 170 deaths had to be observed to detect an expected improvement in median overall survival (OS) from 6.5 to 10 months in Arm A (two-sided α = 5% and β = 20%).

Results 202 patients were included (Arm A, 102; Arm B, 100). Median age, male/female ratio, PS 0–1 and previous surgery were similar in the two arms. After a median follow-up of 44 months, median OS in Arm A was 6.6 months versus 8.0 months in Arm B (p = 0.85). Median progression-free survival was similar between Arms A and B. More grade 3/4 toxicities were observed when LV5FU2-CDDP was administered as a first-line treatment compared with gemcitabine: 79% versus 64% (p = 0.018).

Conclusion This trial did not show any strategic advantage to using LV5FU2-CDDP as a first-line treatment and suggests that gemcitabine remains the standard first-line treatment. Sixty-one per cent of patients were able to receive a second line of chemotherapy.

INTRODUCTION

Pancreatic adenocarcinoma is a highly malignant disease, representing the fifth most common cause of death from cancer in western countries, with <5% of patients still living at 5 years. Only 10–20% of patients are eligible for surgery at diagnosis and approximately half of the remaining patients have a non-resectable tumour."
After the study by Burris et al. showing that gemcitabine-based chemotherapy was more effective than bolus 5-fluorouracil (5FU), the former became the gold standard for systemic treatment of advanced pancreatic cancer. However, the median survival is still only 5.6 months. Numerous studies have tried to increase the efficacy of chemotherapy by combining gemcitabine with other drugs, but none of the regimens evaluated in phase III trials has shown an increase in overall survival (OS). Only one randomised trial including 569 patients comparing gemcitabine with gemcitabine combined with erlotinib showed a modest but significant increase in OS in the erlotinib arm (6.24 months vs 5.91 months) when gemcitabine was combined with erlotinib.

Cisplatin combined with 5FU appears promising in metastatic pancreatic carcinoma, with a 26% response rate with a median survival of 7 months in a phase II trial. In a randomised trial comparing 5FU with 5FU plus cisplatin, FU-CDDP was better than FU for response and progression-free survival (PFS) but not OS. However, this regimen had serious toxic side effects. A phase II study using a combination of 5FU plus cisplatin with a bimonthly LV5FU2-cisplatin schedule (LV5FU2-CDDP) was better tolerated with a promising OS (9 months). As a result, we compared this regimen with gemcitabine alone as first-line treatment. In addition we wanted to explore the role of a second line of treatment for this cancer.

This paper reports the final results of this FFCD (Fédération Francophone de Cancérologie Digestive) phase III trial comparing two successive lines of chemotherapy.

**PATIENTS AND METHODS**

**Patient selection**

Eligibility criteria were: proven metastatic pancreatic adenocarcinoma by histological or cytological biopsy, at least one measurable metastasis $\geq 10 \ mm$ on CT or MRI or $\geq 20 \ mm$ with a conventional scan. The targeted metastasis should not have been treated by radiotherapy. All patients gave written informed consent to participate, were over 18, had a WHO performance status (PS) $\leq 2$, and a life expectancy of $> 2$ months. Adequate bone marrow (absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{l}$, platelets $\geq 100 \times 10^9/\text{l}$), liver function (total bilirubin $< 50 \ \mu\text{mol/l}$, alkaline phosphatases $< \times \text{ULN}$ (upper limit if normal), previous biliary stenting was allowed) and renal function (creatinine clearance $> 60 \ \text{ml/min}$) were required.

Exclusion criteria were: previous palliative or adjuvant chemotherapy, prior radiotherapy $< 4$ weeks, brain metastases, a medical history of malignant tumours, pregnant women or woman who were breast feeding, and locally advanced cancer with no evidence of metastases.

The protocol was approved by the Regional Ethics Committee (Marseille, France).

**Study design and randomisation**

**Clinical and biological investigation**

Pretreatment evaluation included a full medical history, physical examination, haematological and biochemical analysis, including quality of life (QoL) with the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30).

All eligible patients were randomised 1:1 through a minimisation programme at the FFCD centre (Dijon): to either Arm A, LV5FU2-CDDP followed by gemcitabine after progression; or Arm B, gemcitabine followed by LV5FU2-CDDP after progression.

Patients were stratified according to WHO PS (0, 1 vs 2), tumour localisation (head vs other) and participating institutions (centre).

**Treatment plan**

LV5FU2-CDDP included a 2 h infusion of leucovorin (LV) $200 \ \text{mg/m}^2$ followed by 5FU as a bolus $400 \ \text{mg/m}^2$ then a 46 h infusion of $2400 \ \text{mg/m}^2$ with cisplatin $50 \ \text{mg/m}^2$ as a 2 h infusion on day 1, every 2 weeks.

Gemcitabine included $1000 \ \text{mg/m}^2$ as a 50 min weekly infusion for 7/8 weeks and then a weekly infusion for 3/4 weeks according to a classic Burris regimen.

In the case of disease progression during the first line of treatment, second-line chemotherapy was initiated until progression occurred.

**Dose adjustment**

If grade 3 or 4 toxicity occurred treatment was interrupted until toxicity had decreased to $\leq$ grade 2. Treatment was then begun again with a 25% reduction in the initial dosage. If grade 3 or 4 toxicity occurred again treatment was discontinued. Recovery of renal function to grade 0 was necessary to continue cisplatin with a 25% dose reduction.

**Evaluation and follow-up**

All toxicities were graded according to National Cancer Institute common toxicity (NCT-CTC) criteria (v3.0). Serious adverse events were also recorded within 24 h.

After randomisation, a complete clinical examination and full laboratory investigations were performed every 2 weeks. Platelets, white blood cells (WBC) and haemoglobin were collected each week from patients receiving gemcitabine.

Radiological assessment (abdominal and thoracic CT scan) and tumour marker (carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9) evaluations were performed every 8 weeks. The tumour response was classified according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria based on imaging results. After ending treatment, follow-up information including a clinical examination and QoL assessment was available for all patients every 8 weeks until disease progression or death.

**Statistical methods**

This randomised multicentre phase III trial was designed to compare OS as the primary end point. OS was defined as the interval between randomisation and death (all causes). To detect an expected improvement in median OS from 6.5 (Arm B) to 10 months in arm A (two-sided $\alpha = 5\%$ and $\beta = 20\%$), 202 patients had to be included over 52 months (including 5% of lost to follow-up) to observe 170 deaths. The minimum follow-up for the last included patient was 13 months.

Secondary end points included:

- PFS was defined as the interval between randomisation and the first disease progression or death (all causes). Patients alive without progression were censored.
- Second-line PFS (PFS2) was defined as the interval between randomisation and progression or death (all causes) during second-line treatment. Patients alive without progression during second-line treatment were censored. In patients receiving only one line of treatment, PFS2 was defined as the interval between randomisation and the first disease progression or death (all causes).
- Proportion of patients receiving a second line.
- Tolerance for each line.
- The results of QoL assessed by EORTC QLQ-C30 will be presented in a later publication.

All analyses were performed on a strict intent to treat principle. The safety population, defined as all patients receiving at
least one dose of treatment with an available toxicity report, was used to compare toxicities.

Qualitative and continuous variables were described using percentage, means (SD) and medians (minimum — maximum), respectively, and then compared using the χ² or Fisher exact test and the Mann—Whitney test, respectively. Median follow-up was calculated according to the reverse Kaplan—Meier estimates. Survival curves were plotted using Kaplan—Meier estimates and were compared using log-rank tests and stratified log-rank tests. The unstratified and stratified univariate Cox models were used to calculate the HR with a 95% CI. All analyses were performed using Stata software (V10; StataCorp, College Station, Texas, USA) at the 0.05 level of significance.

RESULTS
Between August 2003 and May 2006, in 33 French centres, 102 patients and 100 patients were included in Arm A (first-line LV5FU2-CDDP) and Arm B (first-line gemcitabine), respectively. Three patients in Arm B did not meet the major inclusion criteria and had received prior chemotherapy (two adjuvant and one palliative chemotherapy). Twenty-six patients and 24 patients did not meet minor biological or haematological eligibility criteria in Arms A and B, respectively, and three patients were lost to follow-up in Arm A. However, the 202 patients were included in the intent to treat analyses (figure 1). The median follow-up was 44 months.

Patient characteristics
Patient characteristics are summarised in table 1. Arms A and B were well matched. In Arms A and B the median age was 62 and 65 years and WHO PS 0–1 was 77% and 83%, respectively. Sex, biological markers, prior treatments, and sites of metastases were well balanced. However, one patient in Arm A and two patients in Arm B had received radiotherapy >4 weeks before randomisation. Mean CEA and CA 19-9 levels were also similar in each arm.

TREATMENT DELIVERY
One patient in Arm A and four patients in Arm B did not receive at least one dose of chemotherapy due to complications.

As shown in table 2, the median duration of first-line treatment was significantly longer in patients receiving gemcitabine than in those receiving LV5FU2-CDDP as the first-line treatment: 10 weeks versus 5 weeks (p = 0.0001). Furthermore, the median duration of second-line treatment was significantly longer in patients receiving gemcitabine than in those receiving LV5FU2-CDDP as a second-line treatment: 8 versus 4 weeks (p = 0.044).

Toxicity
The distribution of maximum grade 3/4 toxicities in each arm according to the line of chemotherapy is shown in table 3. This table shows significant differences in haematological grade 3/4 toxicities when LV5FU2-CDDP was administered as the first line of treatment compared with gemcitabine as the first line: 50% in Arm A versus 35% in Arm B (p = 0.03). While no differences were observed for non-haematological and nausea/vomiting grade 3/4 toxicities, the occurrence of all grade 3/4 toxicities was significantly more frequent when LV5FU2-CDDP rather than gemcitabine was administered as the first line of treatment: 79% in Arm A versus 64% in Arm B (p = 0.018).

Figure 1  CONSORT diagram.
Table 1  Patients’ demographics and clinical characteristics.

|                | Arm A (LV5FU2-CDDP in first line) | Arm B (gemcitabine in first line) |
|----------------|-----------------------------------|-----------------------------------|
| n              | %                                 | n                                | % |
| Patients       | 102                               | 100                               |
| Female sex     | 37                                | 36                                | 35 | 36 |
| WHO PS         |                                   |                                   |
| 0              | 28                                | 27                                | 30 | 30 |
| 1              | 51                                | 50                                | 53 | 53 |
| 2              | 22                                | 21                                | 14 | 14 |
| Not determined | 1                                 | 1                                 | 3  | 3  |
| Primary tumour location |                   |                                   |
| Head           | 57                                | 56                                | 49 | 49 |
| Other          | 44                                | 43                                | 50 | 50 |
| Unknown        | 1                                 | 1                                 | 1  | 1  |
| Site of metastases |                   |                                   |
| Liver          | 87                                | 85                                | 90 | 90 |
| Lung           | 15                                | 15                                | 12 | 12 |
| Lymph nodes    | 18                                | 18                                | 24 | 24 |
| Peritoneum     | 11                                | 11                                | 17 | 17 |
| Other          | 7                                 | 7                                 | 8  | 8  |
| Prior treatment |                                  |                                   |
| Chemotherapy   | 0                                 | 0                                 | 3  | 3  |
| Radiotherapy   | 1*                                | 1                                 | 2* | 2  |
| Surgery        | 23                                | 23                                | 27 | 27 |
| Resection      | 13                                | 13                                | 14 | 14 |
| Drainage       | 4                                 | 17                                | 8  | 30 |
| Others         | 6                                 | 6                                 | 26 | 26 |
| Radiological/endoscopic drainage |       | 22                                | 22 | 11 |
| Duodenal stenting |                   | 10                                | 10 | 5  |
| Age (years)    | Median (min–max)                  | Median (min–max)                  | 62 | 84 |
| Biological tumorous marker |           |                                   |
| CEA (ng/ml)    | 9 (0–2224)                        | 7 (1–3604)                        |
| CA 19-9 (UI/ml)| 5650 (0–862200)                   | 5601 (1–156649)                   |

*Radiotherapy >4 weeks before randomisation.

Table 2  Treatment administration

|                | LV5FU2-CDDP | Gemcitabine | p Value* |
|----------------|-------------|-------------|----------|
| Line 1         |             |             |          |
| Arm A          | 102         | 100         |          |
| Arm B          | 15         | 10          | 0.21     |
| Patients with at least 1 administration | 100(99%) | 96 (96%) | 0.001     |
| Median duration of treatment in weeks (n = 96) | 5 (0.496) | 10 (1.164) | 0.0001 |
| Line 2         |             |             |          |
| Arm B          | 100         | 102         |          |
| Arm A          | 15         | 10          |          |
| Patients with at least one administration | 55(55%) | 69 (68%) | 0.11 |
| Median duration of treatment in weeks (n = 53) | 4 (0.17) | 8 (1.21) | 0.044 |

*All two-sided Fisher exact tests or Wilcoxon rank-sum (Mann–Whitney) test.

Table 3  Toxicities according to WHO criteria

|                | LV5FU2-CDDP | Gemcitabine | p Value* |
|----------------|-------------|-------------|----------|
| Line 1         |             |             |          |
| Arm A          | 102         | 100         |          |
| Arm B          | 15          | 10          | 0.21     |
| All toxicities | 80 (79%)    | 61 (64%)    | 0.018    |
| Haematological toxicities | 50 (50%) | 33 (35%) | 0.03 |
| Non-haematological toxicities | 54 (53%) | 44 (46%) | 0.317 |
| Nausea and vomiting | 13 (13%) | 9 (9%) | 0.359† |
| Line 2         |             |             |          |
| Arm B          | 55           | N=69        |          |
| Arm A          | 15          | 10          | 0.21     |
| All toxicities | 38 (69%)    | 51 (74%)    | 0.476    |
| Haematological toxicities | 18 (33%) | 40 (58%) | 0.004 |
| Non-haematological toxicities | 28 (51%) | 35 (51%) | 0.828 |
| Nausea and vomiting | 8 (15%) | 3 (4%) | 0.065† |
| Overall toxicities (lines 1 and 2) | Arm A       | Arm B       |          |
| N              | 102         | 100         |          |
| All toxicities | 87 (86%)    | 77 (80%)    | 0.256    |
| Haematological toxicities | 60 (59%) | 41 (43%) | 0.015 |
| Non-haematological toxicities | 70 (69%) | 60 (63%) | 0.311 |
| Nausea and vomiting | 14 (14%) | 15 (16%) | 0.748 |
| Toxicities grade 3/4 | Line 1 | Line 2 | p |
| LV5FU2-CDDP    | Arm A       | Arm B       |          |
| N              | 69          | N=63        |          |
| All toxicities | 56 (81%)    | 38 (69%)    | 0.16     |
| Haematological toxicities | 41 (59%) | 18 (33%) | 0.004 |
| Gemcitabine    | Arm B       | Arm A       |          |
| N              | 55          | N=59        |          |
| All toxicities | 30 (55%)    | 51 (74%)    | 0.017    |
| Haematological toxicities | 19 (35%) | 40 (58%) | 0.007 |

*All two-side Pearson tests without missing value modality.
†All two-sided Fisher exact tests.

Table 4 shows that 69 patients (68%) and 55 patients (55%) received a second line of chemotherapy in Arms A and B, respectively (non-significant). However, the reasons for the second line of chemotherapy were mainly (p = 0.006) due to progression in Arm B (48 patients, 87%) compared with Arm A (45 patients, 65%). Other reasons for changing the first line of treatment were toxicity in 12 patients in Arm A (17%) and 3 patients in Arm B (6%) (p = 0.006). Others reasons in Arm A were a poor general condition (1 patient), stroke (1 patient), weight loss (1 patient) and unknown (9 patients). Other reasons in Arm B were pain (1 patient) and unknown causes (3 patients).
The second-line treatment was stopped due to disease progression in 44 patients (64%) in Arm A and 34 patients (62%) in Arm B.

**Best response during treatment**

During the first line of treatment in Arm A, 15 patients had an objective response (3 complete responses and 12 partial responses). In arm B, 19 patients had an objective response (3 complete responses and 16 partial responses).

During the second line of treatment, 7 patients had a partial response in Arm A and 4 patients had an objective response (1 complete response, 3 partial responses) in Arm B.

Overall, 19 patients had an objective response (3 complete responses, 16 partial responses) and 39 patients had stable disease in Arm A while 22 patients had an objective response (4 complete responses, 18 partial responses) and 37 patients had stable disease in Arm B. We observed 24 and 17 progressions in Arms A and B, respectively, as the best response. No differences were observed for tumour control according to first or second line of administration (table 4).

**Overall survival**

At the cut-off date, 192 patients had died, 94 (92%) and 98 (98%) in Arms A and B, respectively (table 4). As shown in figure 2, OS did not differ with the treatment sequence (HR 0.97 (95% CI 0.73 to 1.29), log-rank p = 0.83). Median OS was 6.7 months (95% CI 5.4 to 8.6) in Arm A and 8.03 months (95% CI 5.9 to 9.8) in Arm B (figure 2).

The 1 year OS rate was 28.8% (95% CI 20.4% to 37.8%) in Arm A and 32.7% (95% CI 23.7% to 42.0%) in Arm B, and the 2 year OS rate was 7.5% (95% CI 5.2% to 14.1%) in Arm A and 4.1% (95% CI 1.5% to 9.4%) in Arm B.

**Progression-free survival**

At the cut-off date, 69 patients (68%) and 68 patients (68%) had disease progression in Arms A and B, respectively. Moreover, 50 patients in Arm A and 32 patients in Arm B died without reported disease progression. The median PFS was 3.4 months (95% CI 2.4 to 4.4) in arm A and 3.5 months (95% CI 2.4 to 4.1) in Arm B (HR 1.06 (95% CI 0.8 to 1.4), log-rank p=0.67 (figure 3A).

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**Table 4  Response and survival to treatment according to the group of treatment**

|                       | LV5FU2-CDDP | Gemcitabine |
|-----------------------|-------------|-------------|
|                       | N=102       | N=100       |
|                       | n %         | n %         | p Value     |
| Best tumorous response in second line |             |             | 0.8*        |
| Complete response (CR) | 69 0        | 55 0        |             |
| Partial response      | 7 10        | 3 5         |             |
| Stable disease        | 19 28       | 21 38       |             |
| Progression           | 25 38       | 21 38       |             |
| Not evaluable         | 0 0         | 1 2         |             |
| Unknown               | 18 26       | 8 15        |             |
| Best tumorous response in first line |             |             |             |
| Complete response (CR) | 3 3         | 3 3         |             |
| Partial response      | 12 12       | 16 16       |             |
| Stable disease        | 33 32       | 29 29       |             |
| Progression           | 27 27       | 25 25       |             |
| Not evaluable         | 3 3         | 1 1         |             |
| Unknown               | 24 24       | 26 26       |             |
| Overall best tumorous response | 3 3        | 4 4         |             |
| Complete response (CR) | 16 16       | 18 18       |             |
| Partial response      | 39 38       | 37 37       |             |
| Stable disease        | 24 23       | 17 17       |             |
| Progression           | 2 2         | 1 1         |             |
| Not evaluable         | 18 18       | 23 23       |             |
| Progression-free survival (PFS) |             |             | 0.67†       |
| Median PFS in months (95% CI) | 3.4 (2.4 to 4.4) | 3.5 (2.4 to 4.1) |             |
| Median PFS in months (95% CI) after second line | 5.03 (4.3 to 5.9) | 5.8 (4.3 to 7.8) | 0.61†       |
| Overall survival (OS): |             |             |             |
| Median OS in months (95% CI) | 6.7 (5.4 to 8.6) | 8.03 (5.9 to 9.8) | 0.83†       |
| 1 year OS             | 28.8% (20.4% to 37.8%) | 32.7% (23.7% to 42.0%) |             |
| 2 years OS            | 7.5% (3.2% to 14.1%) | 4.1% (1.3% to 9.4%) |             |
| Death                 | 92          | 98          |             |
| Death without registered progression | 30 29 | 32 32 | 0.13*       |
| Alive without registered progression | 3 3 | 0 0 |             |
| Second line           | 69 68       | 55 55       | 0.006*      |
| Patients receiving a second line | 45 65 | 48 87 |             |
| Second line due to progression |             |             |             |

*χ² or Fisher exact test.
†Log-rank test.
LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination.
alternative approaches due to the lack of effective combinations with gemcitabine when this trial was begun. Encouraging results observed with the combination of 5FU plus cisplatin in a phase II trial prompted the initiation of the present phase III trial. The current study shows that OS and PFS were not different in the two arms. Moreover, gemcitabine was better tolerated when administrated as a first-line treatment, with significantly fewer cases of grade 3/4 haematological toxicity. This study confirms that gemcitabine is clearly the standard, with results in this study even better than those in the Burris study.

This is the first randomised phase III trial to evaluate a chemotherapy strategy with a second line of treatment in the treatment plan. At disease progression, the second line was administered in 68% of patients who received first-line LV5FU2-CDDP treatment (Arm A) and in 55% of patients in Arm B. Most Arm B patients received a second line of treatment for progression (87%); in contrast, toxicity was the cause of change in a significant percentage of patients in Arm A (33%), and this difference was statistically significant. The combination of 5FU plus cisplatin caused frequent and sometimes severe nausea and vomiting, even when adequate prophylactic antiemetic treatment was given, and these adverse side effects affected patient compliance and explained the higher percentage of second-line treatments in Arm A. Finally, our results do not support the role of 5FU plus cisplatin as a first line treatment, thus gemcitabine remains the standard of chemotherapy. This study is consistent with recent results published by Colucci et al which showed that gemcitabine plus cisplatin was not superior to gemcitabine alone.

At present, there is no standard in patients with metastatic pancreatic adenocarcinoma that progresses after gemcitabine-based first-line treatment. Although several phase II trials evaluating second-line chemotherapy can be found in the medical literature, definitive conclusions cannot be drawn from these results. Oxaliplatin, a platinum-based compound, is better tolerated than cisplatin which is active in several gastrointestinal tumours. A statistically significant increase in OS was observed with the combination of 5FU plus cisplatin in a phase II trial even better than those in the Burris study. Gemcitabine is the standard, with results in this study even better than those in the Burris study.

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meeting, compared 5FU with 5FU combined with oxaliplatin and showed a significant increase in OS (15 vs 26 weeks; p = 0.014).

This is the first controlled trial to evaluate systematic second-line chemotherapy in patients with disease progression after the first line and its possible influence on OS. A high percentage of patients (61%) were able to receive second-line chemotherapy in this study. However, with only 69 and 55 patients in the respective arms receiving second-line treatment, a dedicated trial to assess specifically the efficacy of second-line treatment could be proposed.

The results seem interesting, with an OS of 8 months in the gemcitabine then LV5FU2-CDDP arm. These results were observed in a multicentre phase III study in unselcted metastatic patients; however, in this setting, the association of 5FU and cisplatin may not be the best choice.

In conclusion this study did not show that LV5FU2-CDDP was better than gemcitabine as the first-line treatment in advanced pancreatic cancer. No significant difference in either FFS or OS was observed between the two treatment arms. Gemcitabine remains the standard for first-line chemotherapy in patients with unresectable metastatic tumours. A platinum-based regimen could be used for second-line treatment and oxaliplatin combined with 5FU seems to be the best candidate.

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