Digestive and Liver Disease 43 (2011) 912–916

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Phase II study of first-line FOLFIRI for progressive metastatic well-differentiated pancreatic endocrine carcinoma

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ARTICLE INFO

Article history:
Received 5 August 2010
Accepted 1 July 2011
Available online 9 August 2011

Keywords:
Chemotherapy
5 Fluorouracile
Irinotecan
Neuroendocrine tumour
Prospective
Survival

ABSTRACT

Background: Pancreatic endocrine carcinomas are rare and heterogeneous. Published results concerning treatment of advanced tumours are inconsistent and responses to standard chemotherapy remain unsatisfactory.
Aim: To investigate the ability of the FOLFIRI regimen to manage progressive unresectable metastatic well-differentiated endocrine carcinomas of the pancreas as first-line chemotherapy.
Methods: 20 patients with metastatic or advanced well-differentiated endocrine carcinomas of the pancreas and progressive disease were enrolled in a prospective multicentre phase II trial to receive chemotherapy with FOLFIRI schedule (irinotecan 180 mg/m^2 infusion combined with simplified LV5FU2) every 14 days. The primary end point was the non-progression rate at 6 months.
Results: The 6-month non-progression rate was 80% (95% confidence interval [56–94%]), with stabilisation in 15 patients and 1 objective response. Overall survival at 24 months was 65% [40–82%]. Median progression-free survival was 9.1 months [6.5–17.3 months]. The median number of administered cycles was 12 [range 1–28]. Grade 3/4 haematologic toxicity occurred in 5 patients (25%) and grade 3 digestive toxicity in 11.
Conclusion: The FOLFIRI regimen, as first-line chemotherapy, achieved stabilisation in most patients whose tumours had been progressing and was well-tolerated. It could be an alternative therapy for advanced well-differentiated endocrine carcinomas of the pancreas.

1. Introduction

Endocrine tumours are rare. Their incidence is 5.3/100,000 inhabitants [1]. These tumours constitute a heterogeneous group in terms of histological characteristics, clinical expression, evolution and prognosis. Histological differentiation, grading and disease stage at diagnosis are the main prognostic factors for survival [1–3].

The treatment of well-differentiated endocrine carcinomas depends on the primary site and tumour burden. Radical surgery is the only curative approach and should be considered for patients with potentially resectable disease, even with metastases [4–7]. For unresectable and progressing well-differentiated endocrine carcinomas of the pancreas, anti-cancer treatments, such as chemotherapy, chemoembolisation or biotherapy are recommended. The classical first-line treatment is based on chemotherapy combining doxorubicin and streptozotocin because of the high response rate (69%) obtained by Moertel et al. [8]. However, their results were not confirmed by later studies [9–11]. Numerous chemotherapies and other treatments (biotherapies, targeted biotherapies, radiotherapy and targeted radionucleide radiotherapy) can been given in this setting and have been included in national and international guidelines (www.tncd.org, www.neuroendocrine.net/guidelines_tnm_classifications.html).
The rarity of these tumours make recruitment of homogeneous and sufficiently large cohorts of patients, to achieve adequate statistical power in clinical trials, difficult.

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1590-8658/$36.00
doi:10.1016/j.dld.2011.07.001

The FOLFIRI regimen (a combination of irinotecan, 5 fluorouracil and leucovorin) was evaluated by Ducreux et al. in a phase II study on 20 patients with pretreated metastatic well-differentiated endocrine carcinomas (including 10 with primary pancreatic tumours). Tumour control was observed in 16 patients with an objective response in 1 patient [12]. Their results were very encouraging because most of the patients had been heavily pretreated and tolerance was good.

The aim of this prospective, multicentre, open, phase II study was to assess the efficacy and toxicity of the FOLFIRI regimen as first line chemotherapy for patients with unresectable and progressing well-differentiated endocrine carcinomas of the duodenopancreatic area.

2. Patients and methods

The protocol was approved by the Regional Ethics Committee of Champagne-Ardenne on 24 June 2003. The study was registered at clinical trial.gov. with reference NCT00416767. Written informed consent was obtained for all patients.

2.1. Patients

Patients with a histologically confirmed unresectable well-differentiated endocrine carcinoma of the pancreas (functional or not) were eligible. Other inclusion criteria were: age between 18 and 80 years, WHO performance status (PS) ≤ 2, measurable locally advanced (>50 mm for primary tumour and/or lymph-node metastases) or metastatic disease (>15 mm for hepatic or extrahepatic metastases), progressive disease (>20% increase of measurable lesions or appearance of new lesions according to RECIST V1.0 criteria) [13] within the 6 months preceding inclusion. Metastases had to be histologically proven or positive on somatostatin-receptor scintigrams.

Histological diagnosis of well-differentiated endocrine carcinoma was based on the 2000 WHO criteria [14]. The Ki-67 index had to be $\leq$15% and the mitotic count <10 for 10 high-power fields. These cut-off have been determined before the ENETS grading classification has been published [15]. ENETS TNM classification was also retrospectively applied [15].

Biochemical and haematological laboratory tests had to be adequate to receive chemotherapy: neutrophil count $\geq 1500/mm^3$, platelets $\geq 100{,}000/mm^3$, creatinine level $\leq 135\ \mu mol/l$ and total bilirubin $\leq 30\ \mu mol/l$.

Patients had to be naive from: chemotherapy, radiotherapy (external or internal) and/or chemoembolisation. External radiotherapy was an exclusion criteria only if it concerned a target. Interferon had to be stopped 3 months before inclusion but somatostatin analogues were allowed for functional tumours.

Non-inclusion criteria were: poorly differentiated endocrine carcinomas, Gilbert's syndrome, pregnancy and breast feeding.

2.2. Clinical and biological work-up

Four weeks before enrolment, pretreatment evaluation included full medical history and physical examination (weight, body surface area, WHO PS), standard haematological and biochemical analyses and dosages of chromogranin A and biomarkers, depending on the clinical history and presentation (gastrin, insulin, C-peptide, glucagon, vasoactive intestinal peptide, somatostatin, thyrocalcitonin, serotonin) and complete morphological evaluation that included chest and abdominal computed-tomography (CT) scans or magnetic resonance imaging (MRI), and somatostatin-receptor scintigraphy.

2.3. Treatment plan

All patients received FOLFIRI chemotherapy, consisting of irinotecan 180 mg/m^2 infusion on day 1 combined with simplified LV5FU2: a single 2-h infusion of leucovorin 200 mg/m^2 on day 1, followed by a 400-mg/m^2 bolus of 5 fluorouracil, then continuous infusion of 5 fluorouracil 2400 mg/m^2 over 46 h. Cycles were scheduled to be repeated every 14 days using a chemotherapy free-interval scheme.

Forty-eight hours before each chemotherapy cycle, haematological and biochemical analyses, physical examination, including body surface area (weight), and WHO PS were done. All toxicities were also assessed using the National Cancer Institute–common toxicity criteria NCI–CTC version 2.0 (available, http://ctep.cancer.gov). Severe adverse events were also recorded within 24 h of their onset.

Treatment was to be stopped when grade 3/4 toxicity persisted after dose reduction or after 3 weeks without treatment because of toxicity, the tumour progressed under chemotherapy, or withdrawal of consent.

When the tumour stabilised, FOLFIRI was prolonged for another 3 months, then a treatment break could be allowed when stabilisation was confirmed and it lasted until progression. During the treatment break, the tumour response was evaluated every 3 months. If the tumour progressed during the chemotherapy free-interval (treatment break), FOLFIRI could be reintroduced and repeated until any toxicity appeared or progression. For a partial response, treatment was continued until stabilisation or progression.

Concomitant supportive and toxicity-preventive treatments (corticosteroids, setrons, atropine and loperamide, haematopoietic-stimulating factors) were allowed.

2.4. Dose adjustment

Treatment adjustment was done as follow: at the first episode of grade 3/4 toxicity, treatment was interrupted until regression $\leq$ grade 2 for haematological toxicity and to grade 0 for gastrointestinal toxicity. Then chemotherapy was pursued with a 20% reduction of the original dose. A second episode of any grade 3/4 toxicity led to a 50% reduction of the original dose. Treatment was definitively stopped if a third episode grade 3/4 toxicity occurred. No dose escalation was permitted. Treatment was stopped if the patient did not recover grade 2 toxicity or within 3 weeks after the planned date of chemotherapy administration.

2.5. Follow-up assessment

The tumour responses were evaluated every 3 months including MRI or CT-scan measurements of the target lesions and were classified according to RECIST v1.0 criteria [13].

The relevant biomarkers were measured every 3 months if they had been elevated at baseline. Biological complete response was defined as normalisation of chromogranin A or other elevated biomarkers levels, partial response as >50% reduction, stabilisation as variation from 25% to 50%, and progression as a >25% increase.

2.6. Statistical methods

All analyses were performed according to intent-to-treat for all included patients, regardless of eligibility criteria and treatment received. The primary end point was the non-progression rate at 6 months defined as the number of patients free of progression 6 months after treatment initiation. Secondary end points included the tumour and biological responses at 6, 12, 18, and 24

Table 1
Characteristics of the 20 patients with metastatic well-differentiated pancreatic endocrine carcinoma.

Characteristics	Value
Age (mean/SD) years	58.1 (12.3)
Men, *n* (%)	13 (65)
WHO performance status ≤2, *n* (%)	18 (90)
Metastase sites, *n* (%)	
Liver	19 (95)
Lungs	1 (5)
Lymph nodes	6 (30)
Peritoneum	1 (5)
Bones	3 (15)
Other	0 (0)
Functional tumour, *n* (%)	5 (25)
MEN 1, *n* (%)	2 (10)
Prior treatment, *n* (%)	
Chemotherapy	0 (0)
Chemoembolisation	0 (0)
External radiotherapy	1 (5)
Surgery	7 (35)
Somatostatin analogues	5 (25)
KI67 ≥ 15%, *n* (%)	3 (15)
Chromogranin A > normal, *n* (%)	12 (60)

SD: standard deviation, MEN 1: multiple endocrine neoplasia type 1.

months, progression-free survival (PFS), time-to-treatment failure (TTF), disease duration control, overall survival (OS) and safety.

PFS was defined as the time from inclusion until the date of first progression or death (any cause); TTF was defined as the time from inclusion until definitive treatment discontinuation because of progression, toxicity or other reasons; disease duration control was defined as the time interval between response or stability and 1st progression or tumour-related death, OS was defined as the time from inclusion until the date of death (any cause) or the last follow-up visit for a surviving patient. Progression rates were reported using frequency and percent with its 95% confidence intervals (CI). Continuous variables are given as using means ± standard deviation (SD) or medians (range). Survival times were estimated using the Kaplan–Meier method and described as medians [95% CI].

Follow-up was calculated using reverse Kaplan–Meier estimation and reported as medians.

Twenty patients had to be enrolled to use Fleming one-step design (5% unilateral alpha type-one error and 80% power) and the following hypotheses: H0 a non-progression rate at 6 months of 60% is no improvement and H1 a non-progression rate at 6 months of 85% is expected [16]. Fleming's decision rules were the following: if we observed 15 or fewer progression-free patients at 6 months, the treatment will be declared not an improvement; if we observed 16 or more progression-free patients at 6 months, the treatment will be declared promising.

Kurskal–Wallis was used to estimate the distribution of the Ki-67 index according to the best response.

3. Results

3.1. Patient's characteristics

A total of 20 patients from 6 French hospitals were included in the study between May 2004 and July 2005. Median follow-up was 31 months (95% CI 29–35). Patient characteristics at inclusion are summarised in Table 1. All were stage IV according to the TNM ENETS classification. The Ki 67 staining was available for 16 patients (insufficient amount of material in 4) and was ≤ 15% in 13 patients. Tumour was non-functional in 15 patients.

Four patients did not meet the major eligibility criteria: 3 patients had Ki-67 index >15% and 1 patient had received prior radiotherapy to the primary tumour, although that lesion was not used as a measurable target.

Table 2
Maximal grade toxicity observed during FOLFIRI chemotherapy (NCI–CTC version 2.0).

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Overall	0	0	4 (20)	10 (50)	6 (30)
Haematological	3 (15)	4 (20)	8 (40)	2 (10)	3 (15)
Leucopenia	11 (55)	5 (25)	3 (15)	3 (15)	0
Neutropenia	6 (30)	5 (25)	4 (20)	2 (10)	3 (15)
Febrile neutropenia	19 (95)	0	1 (5)	0	0
Non haematological	0	2 (10)	5 (25)	10 (50)	3 (15)
Nausea	9 (45)	4 (20)	3 (15)	4 (20)	0
Vomiting	10 (50)	1 (5)	7 (35)	2 (10)	0
Mucositis	14 (70)	5 (25)	0	1 (5)	0

Results are reported as number of patients (%).

3.2. Treatment and its toxicity

All patients received at least 1 chemotherapy cycle. The median number of cycles was 12 [range 1–28]. Median treatment time was 5.3 [range 0–23] months. Eight patients had at least 1 treatment break (6 had 1 and 2 had 2 breaks). During chemotherapy, the WHO PS remained ≤ 2 for all the patients.

A majority of the patients (80%) experienced grade 3/4 toxicity during treatment (Table 2). However, only 6 (30%) patients had grade 4 toxicity: neutropenia for 3, thrombosis for 1, pain for 1 and rhabdomyolysis for 1; 1 patient had grade 2 febrile neutropenia. Treatment was stopped because of toxicity for 4 patients (20%), and dose was reduced for 5 (25%). Global haematologic grade 3–4 toxicity was 25%. No toxic death was recorded. Eight patients developed severe adverse events: pulmonary embolism for 2, melena and rhabdomyolysis for 1, severe diarrhoea with dehydratation for 2, diabetes decompensation for 2, and gastric perforation requiring surgery for 1.

3.3. Response and survival

The non-progression rate at 6 months was 80% (95% CI: 56–94%): stabilisation for 15 patients, objective response for 1, and disease progression in the remaining 4 (Table 3). Then 16 patients were free of progression at 6 months, meaning that regarding Fleming's decision rules, the non-progression rate was significantly higher than the H0 hypothesis of no improvement at 60% ($P = 0.05$).

The 24-month post-inclusion OS was 65% [40–82%] (Fig. 1), the median PFS was 9.1 [6.5–17.3] months (Fig. 2), the median TTF was 6.5 [3.1–15.5] months, the median disease control duration was 8.6 [3.0–24.8] months. It was calculated for 13 of the 20 patients because 2 patient's disease did not progress, 4 patients had tumour progression at the first evaluation, and the last patient's first tumour evaluation was made at 30 months of follow-up.

Twelve of the 16 patients with progressive disease received second-line therapy: chemotherapy for 9, and somatostatin analogue, chemoembolisation or Lipiocis treatment, for 1 each.

Table 3
Tumour responses according to time after starting treatment.

Date of evaluation	Objective response	Stable disease	Progression
6 months	1 (5%)	15 (75)	4 (20)
12 months	0	9 (45)	11 (55)
18 months	0	5 (25)	15 (75)
24 months	0	4 (20)	16 (80)

Results are expressed as number of patients (%).

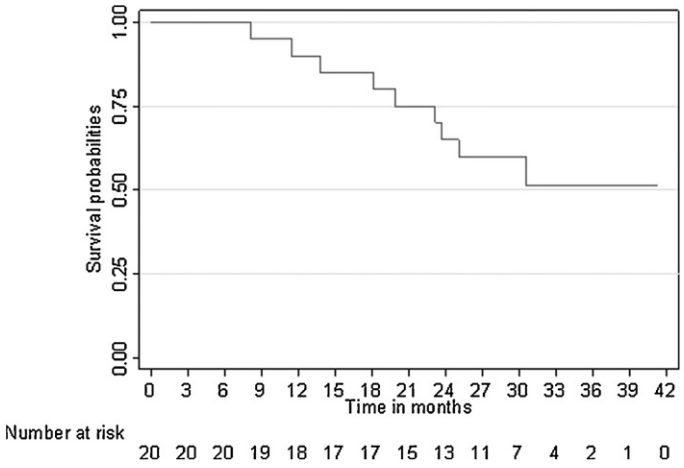

Fig. 1. Overall survival (Kaplan–Meier method).

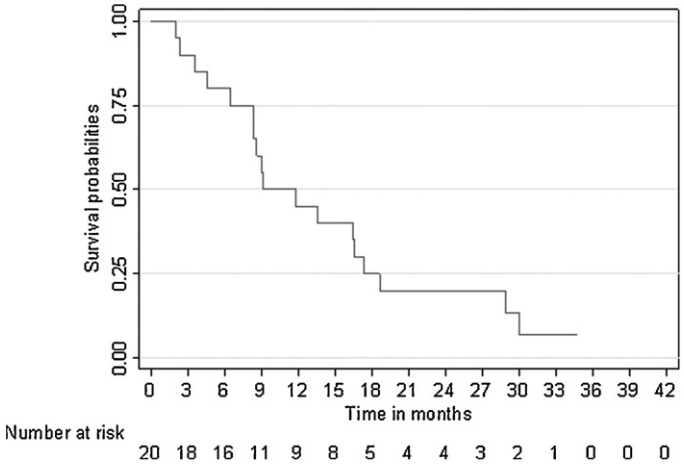

Fig. 2. Progression free survival (Kaplan–Meier method).

At the data cut-off, amongst the 20 patients, 9 died with progression, 9 were alive with progression and 2 were alive without progression.

Chromogranin A levels at baseline were elevated in 12 patients. Partial biological responses were observed in 3, progression in 9 and stability in 4. Radiological responses did not parallel the biological responses. The Ki-67 index, determined for 16 patients, was not predictive of tumour response since Ki-67 distribution did not differ according to the best response during treatment (Kruskal–Wallis $P = 0.29$).

4. Discussion

Progressive unresectable pancreatic NETs have limited treatment options and at the time this study was conducted no chemotherapy has proven high response rate. Moreover data on PFS, duration of stabilisation and OS are heterogeneous when they are available. Thus comparisons of data from these studies with data from the current study are difficult. Although our study included a small number of patients, it was prospective, all patients had histological proven well-differentiated endocrine carcinoma of the pancreas, all were chemotherapy-naive and all had documented disease progression according to the RECIST criteria during the six months preceding enrolment. In previously published studies, these criteria were rarely taken into account.

Our study reached its primary end point: non-progression rate at 6 months was 80% (56–94). Non progression rate is a marker of efficacy because stabililisation leads to improve survival [17–19].

The FOLFIRI regimen has been evaluated in only one previous study to treat endocrine tumours of various primary lesions in pretreated patients [12]. Both studies recorded only 1 objective response amongst their 20 enrolled patients. This result might be considered disappointing compared to the standard chemotherapy regimen (doxorubicin–streptozotocin) with 2 studies that found high response rates (69% and 36%) [8,9], although 2 others showed only 6% objective response rates [10,11], and compared to recent studies with other regimens that gave very enthusiastic results. The combination capecitabine–temozolomide as first-line chemotherapy in patients with advanced neuroendocrine pancreatic tumours gave 70% objective response rates and 27% stabilisation [20]. Two other recent studies performed in patients with different types of advanced neuroendocrine tumours with 5 fluorouracil–cisplatin–streptozotocine [21] and 5 fluorouracil–dacarbazine–epirubicin [22] showed 89–95% tumour control rates in the subgroup of patients with pancreatic tumours, with 38% and 58% objective response rates, respectively.

In our study the PFS was 9.1 months, longer than Ducreux et al.'s [12] (5 months) and within the range obtained with doxorubicin–streptozotocin (from 3.9 months [11] to 15.0 months [9]), but lower than that obtained with other recently evaluated regimens: 17 months to 18 months with 5 fluorouracil–doxorubicin–streptozotocin [23], 5 fluorouracil–dacarbazine–epirubicin [22] and capecitabine–temozolomide [20].

Two recent large studies showed that the targeted therapies sunitinib and everolimus significantly increased PFS as compared to placebo in patients with advanced well-differentiated endocrine carcinomas of the pancreas [19,24]. Although the comparison of our data with the latter studies is debatable, FOLFIRI gave similar results for PFS, 9.1 months versus 11.4 months [19] and 11 months [24], respectively.

Haematological toxicity, especially grade 3/4 neutropenia (25%) was similar to haematological toxicity recorded with doxorubicin–streptozotocin by Delaunoit et al. [9] (24%) and less than that observed in patients given the same regimen for colon cancer [25] (60%) and in the study by Ducreux et al. [12] (40%), but digestive toxicity was similar. We can speculate that the haematological tolerability was better because our patients did not receive chemotherapy previously. Toxicity of targeted therapies is very different [19,24]. The FOLFIRI regimen is easy to use: half-day hospitalisation versus 5 days for the doxorubicin–streptozotocin regimen, and does not lead to renal and cardiac toxicities. Pertinently, the toxicity profile, particularly haematological toxicity, and FOLFIRI regimen efficacy could be improved by the determination of the drug-metabolising enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) polymorphism [26].

FOLFIRI regimen efficacy against colon cancer has been improved by combining it with bevacizumab [27]. Endocrine tumours are known to be highly vascular and to overexpress vascular endothelium growth factor (VEGF) [28,29]. So the rationale for using VEGF-pathway inhibitors to treat endocrine carcinomas is logical. Some encouraging results have also been obtained with bevacizumab against carcinoid tumours [30]. The combination of FOLFIRI regimen and bevacizumab should be tested against unresectable metastatic endocrine carcinomas, as it has been done with other chemotherapies with encouraging results [31,32].

Our patients had few treatment breaks, perhaps because of the low rate of objective responses or because these time-outs were a novel concept in chemotherapy and had not been applied by investigators.

The main weaknesses of the study concerns Ki67 indexes. It was not possible to measure it in 4 patients because of low amount of material and it was above the predetermined threshold in 3 patients. We cannot exclude that it might have influenced results. However, all tumours were well-differentiated. Ki67 has not been measured or taken into account in the most recently published studies on chemotherapy [20] and on targeted therapies [19,24], probably because its determination has been considered a standard only recently [15]. Furthermore the low amount of tissue material is a frequent drawback. Five patients previously received somatostatin analogues. It has been recently shown in the randomised placebo-controlled PROMID study that octreotide has a significant antitumour effect for well-differentiated endocrine carcinomas of the intestine [33]. Although this effect might also exist for well-differentiated endocrine tumours of the pancreas, it is much improbable that it has influenced the results of our study.

In conclusion, the FOLFIRI regimen induced stabilisation in most patients with progressive, chemotherapy-naive, well-differentiated endocrine carcinomas of the pancreas but only 1 objective response. It can be done on ambulatory hospitalisation. The toxicity profile can be improved by determination of the drug metabolising enzyme. This regimen could be an alternative to other chemotherapies or targeted therapies as a first-line therapy should the other drugs be contraindicated. Combination of targeted therapies and chemotherapies should be further evaluated, FOLFIRI regimen could be a good option.

Sources of support

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. Irinotecan was provided by Pfizer.

Conflict of interest statement

Hedia Brixi-Benmansour, Jean-Louis Jouve, Franck Bonnetain, Bruno Landi, Olivia Hentic, Laurent Bedenne: no conflict of interest that could be perceived as prejudicing the impartiality of the research reported; Guillaume Cadiot and Emmanuel Mitry: fees from Pfizer.

Acknowledgements

The authors thank the other investigators: I. Sobhani, J. Taieb, the members of the Scientific Committee: V. Boige, O. Bouché, C. Lombard-Bohas, J.F. Seitz, D. Smith and J. Jacobson for reviewing and constructive remarks.

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