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ORIGINAL ARTICLE

FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study

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Abstract
Purpose The purpose of the present study was to evaluate the activity and the tolerability of the FOLFIRI regimen, administered as second-line chemotherapy in patients with locally advanced or metastatic pancreatic cancer after the failure of a gemcitabine-based regimen.
Methods Patients with locally advanced/metastatic disease who received a first-line chemotherapy (one line only) with gemcitabine ± platinoid (cisplatin, oxaliplatin) and who had measurable disease conform with the RECIST criteria were eligible for the study. FOLFIRI consists of irinotecan 180 mg/m^2 iv on day 1, leucovorin (l-form) 200 mg/m^2 iv on day 1 and 2, 5-FU 400 mg/m^2 iv bolus on days 1 and 2, and 5-FU 600 mg/m^2 iv by ci for 22 h on days 1 and 2, repeated every 2 weeks. The primary end point was the response rate.
Results Among the 50 enrolled patients, 4 partial responses (PR) (8 %) and 14 stable diseases were observed, for a disease control rate of 18/50 (36 %). Forty-one patients (82 %) have been pretreated with cisplatin/oxaliplatin+gemcitabine as first-line chemotherapy. The median progression-free and overall survivals were 3.2 and 5 months, respectively. The 6-month survival rate was 32 %. Grade 3–4 neutropenia and diarrhea occurred in 10 (20 %) and 6 (12 %) patients, respectively.
Conclusion The FOLFIRI regimen showed a modest clinical activity in this quite heavily pretreated patients'

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population with locally advanced or metastatic pancreatic cancer with a manageable toxicity profile.

Keywords Pancreatic cancer · FOLFIRI · Chemotherapy · Second-line · Irinotecan

Introduction

Palliative chemotherapy represents the only treatment option for the vast majority of pancreatic cancer patients, due to the low resectability rate of this deadly disease [1].

Until very recently, gemcitabine monotherapy or its combination with capecitabine or platinoids was considered as standard first-line option, albeit no gemcitabine-based doublet was identified as clearly superior to gemcitabine alone in randomized trials [2–5].

More recently, a new combination based on oxaliplatin, irinotecan, and fluorouracil (FOLFIRINOX) has shown superior results compared to gemcitabine alone and despite its greater toxicity profile is now considered a new first-line standard of treatment, at least in selected patients [6, 7]. After first-line chemotherapy failure, there is no standard second-line therapy of benefit, even if a considerable amount of patients has a good performance status and a relatively low tumor burden [8]. We report here our experience with the FOLFIRI regimen, a potentially non-cross resistant option, as second-line therapy after the failure of a gemcitabine ± a platinum compound-based treatment.

Patients and methods

Patients

Patients with pathologically confirmed, locally advanced, metastatic pancreatic cancer who received a first-line chemotherapy (one line only) with gemcitabine ± platinoid (cisplatin, oxaliplatin) and who had measurable disease conform with the RECIST criteria were eligible for the study.

Other eligibility criteria included: P.S. ECOG 0–1, age ≥18 years and <75 years, at least 4 weeks since completion of any radiation therapy (measurable tumor mass had to be outside the radiation field), and adequate organ function, as indicated by a WBC count ≥3,000/μL, hemoglobin level ≥9 g/dL, platelet count ≥100,000/μL, alkaline phosphatase level ≤5 times the upper limit of normal (ULN), total bilirubin level ≤2 times ULN, serum transaminase level ≤5 times ULN, and creatinine level ≤1.5 mg/dL. Approval of the protocol by each local Independent Bioethical Committee was mandatory, and a written informed consent was required by every enrolled patient.

Treatment

FOLFIRI consists of irinotecan 180 mg/m^2 iv on day 1, leucovorin (l-form) 200 mg/m^2 iv on days 1 and 2, 5-FU 400 mg/m^2 iv bolus on days 1 and 2, 5-FU 600 mg/m^2 iv by ci for 22 h on days 1 and 2 (=one cycle) repeated every 2 weeks.

The use of antiemetic prophylaxis was decided locally.

Patients who developed a severe cholinergic syndrome received preventive treatment with atropine (0.25 mg subcutaneously) during all subsequent cycles.

Patients who developed late-onset diarrhea received high-dose loperamide following specific guidelines.

For any patient with severe toxicity, therapy had to be delayed until complete normalization, and the dose of 5-FU and irinotecan had to be reduced to 80 % of the previous dose for all further administrations.

Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment was offered to all subjects.

Treatment consisted of 4 combination-chemotherapy cycles, and in case of stable or responsive disease, other 4 cycles were administered. Further cycles were administered at investigators' discretion for up to 6 months.

Study evaluations

Evaluations before treatment consisted of a complete medical history and physical examination, assessment of performance status, laboratory exams, including hematologic and biochemical tests (within 7 days of study drug start), computed tomography or magnetic resonance imaging of the abdomen or other body areas with disease involvement, and chest X-ray (within 28 days of study drug start).

During treatment, complete physical examination, including performance status and weight, vital sign, and laboratory tests were recorded at each cycle. Radiological assessment for tumor measurement (RECIST 1.1) [9] was done every 4 cycles in the chemotherapy phase until disease progression.

Response criteria and toxicity

The RECIST response criteria were used [9]. A complete response was defined as the disappearance of all measurable and evaluable disease for at least 4 weeks. A partial response (PR) was at least a 30 % decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. Progressive disease was defined as at least a 20 % increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Stable disease (SD) was neither a

sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. Survival duration was measured from the initiation of therapy to death or to the last follow-up assessment. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 4.0 [23].

Statistical analyses

According to Simon's design (RR not of clinical interest ≤10 %, clinically relevant ≥20 %) [10], 18 consecutive patients were initially treated.

In case of no or one only response achieved, the study should be closed.

In case of >1 response, the accrual should be continued to a total of 42 patients (α 5 %, β 90 %).

Progression-free survival (PFS) was calculated from the start of treatment to the 1st day of progression or drug discontinuation.

Overall survival OS was measured from the 1st day of treatment to the date of death or last follow-up.

OS and PFS were calculated using the Kaplan-Meyer method [11].

Results

Between January 2010 and August 2011, 50 patients were included into the study. After the 42 planned patients as for the Simon's design, 8 additional patients were allowed to enter the study because they were all screened and registered within 10 days from the last (42 nd) patients and before the formal closure notification to all the participating centres. There were 24 male and 26 female patients (female/male ratio, 1:08). Median age was 63 years (range, 47–80). Baseline performance status, according to ECOG, was 0 for 29 patients and 1 for 21 patients.

Level of disease accounted for locally advanced cases in 13 patients (26 %) and metastatic disease in 37 (74 %). Thirty-two out of 37 (86 %) patients with metastatic disease had liver metastases. Primary tumor site was pancreatic head in 34 patients (68 %), body in 13 patients (26 %), and tail in the remaining 3 patients (6 %).

First-line chemotherapy previously administered was GEMOX in 32 patients, CDDP/GEM in 9 patients, GEM alone in 8 patients, and GEM/CAPE in 1 patient.

Chemotherapy regimen was administered for a median of 4 cycles (range, 1–16). Overall response and survival are depicted in Table 1. All the four partial responders had metastatic disease and three out four were responsive to prior GEMOX treatment. Six-month survival was 32 %. Forty-nine patients were available for toxicity assessment.

Toxicity was manageable with a total of 21 patients experiencing at least one episode of grade 3 side effects and 6 patients a grade 4 episode, respectively. One case of febrile neutropenia occurred; no toxic death was reported. The main toxicities are outlined on Table 2.

Discussion

A limited amount of drugs has shown clinical activity and measurable benefits for patients with advanced pancreatic cancer after the failure of a gemcitabine-based first-line chemotherapy [12]. In this setting, irinotecan monotherapy was studied by Yi et al. [13]. Among 33 eligible patients, 3PR and 13 SD were achieved for a DCR of 48 % with manageable toxicity.

Gebbia et al. [14] performed a retrospective analysis in 40 patients with refractory disease recording 6 PR and 14 SD (DCR 50 %) with grade 3–4 diarrhea and mucositis

Table 1 Overall response rate and survival data

	$N = 50$	%	95 % Confidence interval
Partial response	4	8	0.5–15.5
Stable disease	14	28	
Disease control rate (PR+SD)	18	36	22.7–49.3
Progressive disease	26	52	
Not evaluable*	6	12	
PFS (months) median, 3.27; range, 1–11			
OS (months) median, 5.0; range, 1–17			

* Six patients did not complete 4 cycles of treatment due to early progression (5 patients) and consent withdrawal before starting chemotherapy (1 patient). All six are considered as PD in the ITT analysis)

Table 2 Toxicity (G3/G4 grade)

	$N = 49$*	%
Hematologic TOXICITY		
Neutropenia	10 (3)^	20
Thrombocytopenia	1	2
NON-Hematologic TOXICITY		
Asthenia	3 (1)^	6
Alopecia	3	6
Mucositis	2 (1)^	4
Hepatic	5 (2)^	10
Nausea/vomiting	3	6
Diarrhea	6 (2)^	12

* One patient never started chemotherapy

^ Grade 4

Table 3 FOLFIRI regimen in advanced pancreatic cancer

Author	Patients	Pretreatment	IRI dosage	RR (%)	DCR (%)	PFS (months)	OS (months)	6 months OS %	Toxicity (grade 3–4) %
GISCAD (present study)	50	Gemcitabine 8, gemcitabine+oxaliplatin/cisplatin 41, capecitabine/gemcitabine 1	180 mg/m^2 q2wks	8	32	3.2	5.0	32	55
Yoo [15]	31	Gemcitabine 4, gemcitabine/capecitabine 20, gemcitabine/cisplatin 3, gemcitabine/erlotinib 4	70 mg/m^2 d1,3 q2wks	0	23	2.1	4.2	27	38
Neuzill [18]*	70	Gemcitabine/platinum based	180 mg/m^2 100 mg/m^2 d1,3 q2wks	8	43	5.8	6	24 % (12 months)	25.7
Gebbia [14]*	40	Gemcitabine only	180 mg/m^2 q2wks	15	50	3.7	6	NS	25
Taieb [16]	40	Only 1 patient chemo-pretreated	90 mg/m^2 d1,3 q2wks	45	37.5	5.6	12.1	NS	Neutropenia 35 %
Cereda [17]	34	Gemcitabine 34	180 mg/m^2 q2wks	NS	12	2	4.2	NS	Neutropenia 9 %

* Retrospective studies, *NS* = not stated

experienced by 15 and 10 % of patients, respectively. A modified FOLFIRI regimen (FOLFIRI.3) was studied by Yoo et al. [15] in a randomized phase II study versus a modified Folfox regimen. Among the 31 patients treated with the FOLFIRI.3 regimen, a DCR of 23 % and a 6-month survival of 27 % were achieved. Similar encouraging results were reported, in first-line treatment, with a little more intensive version of FOLFIRI.3 by Taieb et al. [16]. On the contrary, Cereda et al. [17] reported substantially negative results with the FOLFIRI or XELIRI regimens in 34 gemcitabine-resistant patients, with 4 SD only and a median survival of 4 months. Finally, a large retrospective French study was recently presented, involving 70 patients previously treated with gemcitabine- and platinum-based chemotherapies, 60 received FOLFIRII, and 10 FOLFIRI.3. A DCR of 44 % was obtained with mild toxicity. one-year survival was 17 % [18].

Our results, obtained in a multicenter community setting, seem to further support the role of the combination of irinotecan and fluorouracil as a second-line option for previously treated pancreatic cancer. Toxicity was manageable with no toxic death reported. Our results seem in line with other similar experience with irinotecan and fluorouracil-based regimens as summarized in Table 3. Even if we have not reached our planned goal of a response rate of at least 10 %, it should be outlined that 41 out of 50 patients (82 %) in our study were pretreated with a gemcitabine+platinoids regimen and only a minority received gemcitabine alone, as allowed in our entry criteria. The lack of cross-resistance between gemcitabine/platinoids combinations and FOLFIRI further outlines its potential role as preferred second-line treatment in this patient population.

In our study, one out of three patients benefitted from the FOLFIRI treatment with mild toxicity. However, for patients pretreated with gemcitabine only, combinations of oxaliplatin and fluoropyrimidine still represent an equally reasonable option [19, 20].

Two potential limitations of our study are represented by the inclusion of locally advanced disease along with metastatic patients. Nowadays, separate trials for these two distinct populations are preferred. A second point of weakness is the lack of a quality of life assessment, in order to better define the palliative effect of the FOLFIRI regimen.

It is clear that little progress has been achieved so far in the second-line treatment of pancreatic cancer. Nevertheless, novel agents with innovative mechanism of action are just around the corner like nab-paclitaxel [21] and newer target therapies as mek inhibitors [22].

These drugs will probably help us in transforming advanced pancreatic cancer into a chronic disease, which remains at the moment one of the more important challenge for modern oncology.

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Conflict of interest None.

References

1. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS (2007) National failure to operate on early stage pancreatic cancer. Ann Surg 246:173–180
2. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, Dapretto E, Manzione L, Piazza E, Sannicolò M, Ciaparrone M, Cavanna L, Giuliani F, Maiello E, Testa A, Pederzoli P, Falconi M, Gallo C, Di Maio M, Perrone F; Gruppo Oncologico Italia Meridionale (GOIM), Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD), Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) (2010) Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. J Clin Oncol 28:1645–1651
3. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A, GERCOR, GISCAD (2005) Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 23:3509–3516
4. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W, National Cancer Institute of Canada Clinical Trials Group (2007) Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25:1960–1966
5. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP (2009) Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27:5513–5518
6. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, Groupe Tumeurs Digestives of Unicancer, PRODIGE Intergroup (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
7. Ko AH (2011) FOLFIRINOX: a small step or a great leap forward? J Clin Oncol 29:3727–3729
8. Boeck S, Heinemann V (2008) The role of second-line chemotherapy after gemcitabine failure in patients with advanced pancreatic cancer. Future Oncol 4:41–50
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
10. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
11. Kaplan EL, Meier P (1961) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
12. Custodio A, Puente J, Sastre J, Díaz-Rubio E (2009) Second-line therapy for advanced pancreatic cancer: a review of the literature and future directions. Cancer Treat Rev 35:676–684
13. Yi SY, Park YS, Kim HS, Jun HJ, Kim KH, Chang MH, Park MJ, Uhm JE, Lee J, Park SH, Park JO, Lee JK, Lee KT, Lim HY, Kang WK (2009) Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer. Cancer Chemother Pharmacol 63:1141–1145
14. Gebbia V, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G (2010) Irinotecan plus bolus/infusional 5-fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the Gruppo Oncologico Italia Meridionale. Am J Clin Oncol 33:461–464
15. Yoo C, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, Lee SS, Seo DW, Lee SK, Kim MH, Han DJ, Kim SC, Lee JL (2009) A randomised phase II study of modified FOLFIRI.3 versus modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. Br J Cancer 101:1658–1663
16. Taïeb J, Lecomte T, Aparicio T, Asnacios A, Mansourbakht T, Artru P, Fallik D, Spano JP, Landi B, Lledo G, Desrame J (2007) FOLFIRI.3, a new regimen combining 5-fluorouracil, folinic acid and irinotecan, for advanced pancreatic cancer: results of an Association des Gastro-Enterologues Oncologues (Gastroenterologist Oncologist Association) multicenter phase II study. Ann Oncol 18:498–503
17. Cereda S, Reni M, Rognone A, Ghidini M, Belli C, Longoni S, Fugazza C, Brioschi M, Nicoletti R, Balzano G, Passoni P, Villa E (2010) XELIRI or FOLFIRI as salvage therapy in advanced pancreatic cancer. Anticancer Res 30:4785–4790
18. Neuzillet C, Hentic O, Rousseau B, Rebours V, Bengrine Lefèvre L, Raymond E, Ruszniewski P, Louvet C, Hammel P (2011) FOLFIRI regimen as second-/third-line chemotherapy in patients with advanced pancreatic adenocarcinoma refractory to gemcitabine and platinum salts: a retrospective series of 70 patients. J Clin Oncol 29 (suppl 4 abstract):272
19. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, Riess H, Oettle H (2011) Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer 47:1676–1681
20. Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA (2008) Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 113:2046–2052
21. Hosein PJ, de Lima Lopes G Jr, Pastorini VH, Gomez C, Macintyre J, Zayas G, Reis I, Montero AJ, Merchan JR, Rocha Lima CM (2012) A phase II trial of nab-paclitaxel as second-line therapy in patients with advanced pancreatic cancer. Am J Clin Oncol Feb 2. (Epub ahead of print)
22. Dimou AT, Syrigos KN, Saif MW (2011) Novel agents in the management of pancreatic adenocarcinoma: phase I studies. Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 20–22, 2011. JOP 12:114–116
23. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services (2010) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE), ver 4.03, June 2010. (URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)