XELIRI or FOLFIRI as Salvage Therapy in Advanced Pancreatic Cancer

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Abstract. *Background: More than half of patients with pancreatic adenocarcinoma (PA) are candidates for further treatment when they experience upfront treatment failure. Patients and Methods: Patients with gemcitabine-resistant PA, age <76 years and Karnofski performance status (KPS) >50 were treated with a XELIRI or FOLFIRI regimen until progressive disease or a maximum of six months. As this was an observational study, no statistical design was performed. Results: Between July 2007 and December 2009, 34 patients (median age 60 years; median KPS 90) were treated with XELIRI (26) or FOLFIRI (8) regimen. Grade >2 toxicity consisted of neutropenia in 9% of patients, anemia and fatigue in 3% and hand-foot syndrome in 12%. Median progression-free survival was two months (range 1-4). Maximum response was stable disease in four patients (12%). Median survival was 4.2 (range 1-15) months. Conclusion: Fluoropyrimidine and irinotecan combination does not seem to have any role in the treatment of gemcitabine-resistant PA.*

Virtually all patients with locally advanced or metastatic pancreatic adenocarcinoma present progressive disease (PD) during or immediately after first-line chemotherapy (1, 2). At time of failure, approximately half of patients maintain a good performance status (PS) and are willing to undergo further treatment. While gemcitabine or gemcitabine-based chemotherapy are routinely used as first-line treatments, no universally accepted second-line therapy exists and the therapeutic arsenal for both first-line and salvage therapy in pancreatic cancer is limited. Salvage treatment after gemcitabine-based chemotherapy failure is currently being investigated with mixed success (3-18). A randomized phase II trial has suggested that salvage chemotherapy may improve survival when compared to best supportive care (17). Furthermore, salvage treatment achieves a clinically significant improvement in quality of life in several domains (18). The identification of active drugs and regimens for second-line chemotherapy is therefore needed to provide more treatment opportunities to patients with gemcitabine-refractory pancreatic cancer. Irinotecan, a camptothecin analog, has been demonstrated to have a strong growth-inhibiting effect on cultured pancreatic adenocarcinoma cells (19). Irinotecan monotherapy has been tested in untreated pancreatic cancer patients, yielding a response rate of 9-27% and a median survival of 5.2-7.3 months (20, 21). Fluorouracil is an old drug which, despite its modest activity, is largely used against gastrointestinal solid tumors including pancreatic cancer (1). Capecitabine is a more recently established oral fluoropyrimidine, a prodrug, which is enzymatically converted to fluorouracil within tumor cells, presenting a similar activity and toxicity profile to fluorouracil (22). Single-agent capecitabine has been demonstrated to be a safe treatment option in gemcitabine-pretreated patients with advanced pancreatic cancer, reporting a median time to progression and a median survival of 2.3 and 7.6 months, respectively (5). *In vitro* and *in vivo* studies have demonstrated a synergism between irinotecan and fluoropyrimidines (22-26).

Since fluoropyrimidine and irinotecan are gemcitabine non-cross resistant drugs (25), both licensed in Italy for the treatment of advanced pancreatic cancer, this study explored their activity as salvage therapy after gemcitabine-based chemotherapy failure.

Patients and Methods

Patient population. Patients aged 18 to 76 years, with Karnofski performance status >50, with cytologically or histologically proven advanced pancreatic adenocarcinoma, adequate bone marrow (absolute neutrophil count (ANC) ≥1,500 cells/mm^3; platelet count ≥100,000 cells/mm^3 and hemoglobin ≥10 g/dl); kidney (serum creatinine ≤1.5 mg/dl) and liver function (serum total bilirubin ≤1.5 mg/dl and serum

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transaminases ≤5 upper limit of laboratory normal) and PD after at least one prior gemcitabine-based chemotherapy were submitted to salvage treatment with either XELIRI (irinotecan 200 mg/m^2 day one and capecitabine 2,000 mg/m^2 day one to fourteen every 21 days) (25) or FOLFIRI (irinotecan 180 mg/m^2, lederfolin 200 mg/m^2, 5-fluorouracil (5-FU) 400 mg/m^2 bolus on day one plus 48-hour intravenous infusion of 5-FU 2,400 mg/m^2 every two weeks) (22) regimens. The decision whether to treat patients with fluorouracil or capecitabine was based on medical choice due to the prior presence of central venous catheter or to the risk of the patient to thrombotic or infectious events or to logistic considerations (*i.e.* distance of patient's residence from the hospital) or influenced by patient's choice.

Treatment plan. XELIRI or FOLFIRI regimen was administered until PD, unacceptable toxicity, patient refusal or medical decision to continue treatment, or a maximum of six months was reached. Assessment of disease, including CA19.9 measure and high-resolution contrast enhanced computed tomography scan of the abdomen and chest was performed at baseline, every eight weeks during chemotherapy and after its conclusion, or when PD was clinically suspected. Complete blood, platelet and differential counts were performed before every administration, while a biochemistry profile was performed on a three-weekly basis.

Tumor assessment, dose modification and statistical methods. As this was an observational study, no statistical design or sample size calculation was performed. Descriptive analyses of radiological and biochemical response rate, progression-free survival (PFS) and overall survival (OS) were reported. Patients with at least one measurable indicator lesion according to RECIST criteria were considered assessable for response evaluation (27). Biochemical response for patients with a CA19.9 serum basal value greater than normal was assessed on the basis of CA19.9 change at nadir, as previously described (28). Namely, a CA19.9 reduction <50% was defined as non-response, a reduction by 50%-89% as minor biochemical response; and a reduction >90% as major biochemical response. PFS was calculated as the interval between the initiation of treatment and the occurrence of PD or death, whichever occurred first, and OS was measured from initiation of treatment to date of death or to the last follow-up assessment. All participating patients were required to give written informed consent. Hydration, anti-emetic treatment and drug dilution, as well as guidelines for dose-reduction and treatment delay have been previously described (22, 25). Toxicity was graded according to the NCI-CTC version 3.0 (29). All probability values were from two-sided tests. Statistical analyses were performed with the Statistica 4.0 statistical package for Microsoft Windows.

Table I. *Patient characteristics at baseline*.

Characteristic	N (%)
Treatment received	34
XELIRI regimen	26 (76)
FOLFIRI regimen	8 (24)
Age (years)	
Median	60
Range	32-72
Gender	
Male	22 (65)
Female	12 (35)
Karnofsky PS	
70-80	6 (18)
90-100	28 (82)
Stage	
III	1 (3)
IV	33 (97)
Lesion site	
Pancreas	29 (85)
Liver	27 (79)
Lung	10 (29)
Peritoneum	12 (35)
Abdominal nodes	3 (9)
Bone	3 (9)
Number of lesions	
1	1 (3)
2-5	10 (29)
>5	23 (68)
Median CA19.9 (UI)	1306 (range 1-17093)
>ULN	32 (94)
<ULN	2 (6)
Prior therapy	
Pancreatic surgery	9 (26)
Radiotherapy	14 (41)
Chemotherapy	34 (100)
I line	34 (100)
II line	17 (50)
III line	2 (6)

PS: Performance status; N: number; ULN: upper limit of normality.

Results

Patient population. Between July 2007 and December 2009, 34 patients with progressive pancreatic adenocarcinoma after gemcitabine-based chemotherapy were treated at the host institution with either a XELIRI (26) or FOLFIRI (8) regimen (Table I). Baseline CA19.9 was elevated in 32 patients (94%). Previous treatment consisted of chemotherapy with single agent gemcitabine or capecitabine (N=6) or a four-drug therapy (PEXG or PDXG: cisplatin, epirubicin or docetaxel, capecitabine and gemcitabine (30)) (N=28); 17 (50%) patients received a second-line chemotherapy with: PEXG regimen (N=13), ifosfamide and mitomycin (6) (N=1), GEMOX (14) (N=1) and gemcitabine (N=2). Two patients received a third-line with gemcitabine (N=1) and etoposide plus cyclophosphamide (N=1) as well.

In six cases, prior chemotherapy was administered as adjuvant treatment after surgery with radical intent (gemcitabine; N=4; PEFG: cisplatin, epirubicin, fluorouracil, gemcitabine; N=1; PEXG; N=1). Median time to relapse was 11.3 months (range 7.5-13.2). Median previous PFS, which was calculated as the interval between the start of the previous chemotherapy and the radiological demonstration of PD or recurrence preceding XELIRI or FOLFIRI administration, was 4.1 months (range 1.5-9 months) and only nine patients (26%) had previous PFS >six months.

Table II. *Toxicity (%) per cycle (and per patient).*

Toxicity (%)	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	8 (12)	16 (29)	2 (6)	1 (3)
Platelets	28 (38)	4 (9)	0 (0)	0 (0)
Hemoglobin	61 (70)	12 (18)	1 (3)	0 (0)
Stomatitis	6 (18)	1 (3)	0 (0)	0 (0)
Vomiting	7 (23)	4 (12)	0 (0)	0 (0)
Nausea	19 (59)	1 (3)	0 (0)	0 (0)
Diarrhea	7 (23)	1 (3)	0 (0)	0 (0)
Fatigue	10 (26)	6 (12)	1 (3)	0 (0)
Liver	8 (18)	1 (3)	0 (0)	0 (0)
Hand-foot syndrome	3 (9)	4 (12)	6 (12)	0 (0)

Table III. *Activity and efficacy analyses summary.*

Outcome measure	No. (%)
CA19-9 response	
Reduction <50% basal value	32 (100)
Reduction >50% and <89% basal value	0 (0)
Reduction >89% basal value	0 (0)
Best response	
Partial response	0 (0)
Stable disease	4 (12)
Progressive disease	30 (88)
Median PFS (months)	2.0 (range 2-4)
6-month PFS	0%
Median OS (months)	4.2 (range 1-15)
1-year OS	6%

Median time between the start of the first-line chemotherapy and the radiological demonstration of PD or recurrence preceding XELIRI or FOLFIRI administration was 8.7 months (range 3-27.6 months).

Treatment summary. A total of 107 cycles (70 XELIRI; 37 FOLFIRI) were administered. The median duration of chemotherapy was three cycles (range 1-9). Dose intensity of fluorouracil, capecitabine and irinotecan was over 80% of the total planned dose. Therapy was discontinued prior to completion in all patients due to radiological PD (26), clinical deterioration (6) or toxicity (2).

Safety and activity analysis. Treatment-related toxicity was mild. Grade >2 toxicity consisted of neutropenia in 9% of patients, anemia in 3%, fatigue in 3% and hand-foot syndrome in 12% (Table II). Two patients interrupted treatment due to severe colinergic reaction and stroke.

Median PFS was two months (range 1-4). Six patients were not assessed for radiological response due to early clinical deterioration. In these cases, PFS was calculated as the interval between treatment start and death. Maximum response was stable disease in four patients (12%) lasting for six months in one patient. Maximum CA19.9 reduction was approximately 30% in 3/32 patients (9%). All patients died of PD. Median and one year survival were 4.2 months (range 1-15) and 6%, respectively (Table III).

Discussion

The combination of fluoropyrimidine and irinotecan was explored as salvage therapy in patients with advanced pancreatic cancer experiencing PD after gemcitabine-containing chemotherapy. No antitumor activity was observed as no patient was free of progression at six months and only 6% of patients were alive at one year from start of salvage treatment.

Irinotecan is a camptothecin analogue, largely used in the treatment of advanced colorectal cancer in association with fluoropyrimidine due to its synergistic activity *in vivo* and *in vitro* (22-25).

As single agent therapy, irinotecan has demonstrated interesting activity in chemo-naïve patients affected by pancreatic cancer with response rate of 9-27% and median survival of 5.2-7.3 months (20, 21). However, in the first-line setting, two phase III trials (31, 32) of irinotecan and gemcitabine combination chemotherapy showed a modest activity with a response rate of 15-16%, a median PFS of 2.8-3.5 months and a median OS of 6.4 months, failing to obtain a survival benefit over gemcitabine monotherapy.

Also the association of irinotecan with cisplatin did not demonstrate encouraging results with 5% of partial responses and median PFS and OS of 3.1 and 5 months respectively, reporting an unexpected toxicity too (33).

Only recently, a randomized phase III trial comparing the combination of fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX regimen) with gemcitabine as a first-line treatment in metastatic pancreatic cancer has obtained a significant survival improvement for combined therapy with a median PFS and OS of 6.4 and 10.5 months, respectively (34). Also in this case, toxicity profile was worrisome and poorly acceptable in the perspective of the palliative purpose of treatment.

Other interesting results have been reported, in a few phase II studies, when irinotecan was combined with gemcitabine, 5-FU, cisplatin and leucovorin (G-FLIP regimen) (35) or in two-drug combinations with fluorouracil, docetaxel or S1 (25, 36, 37) or finally in triple association with 5-FU and gemcitabine or gemcitabine and celecoxib (38, 39), yielding response rates of 7-44%, median PFS of 3.4-8.2 months and median OS of 8.1-12.1 months (25, 35-39) and demonstrating to be feasible regimens with

acceptable toxicity profiles. However, none of these regimens have been tested in a phase III trial against standard treatment.

Second-line chemotherapy with single agent irinotecan has been demonstrated to be a marginally effective and well tolerated regimen for gemcitabine-pretreated advanced pancreatic cancer patients reporting response rates <10% and median OS of 4-6.6 months (40, 41). Irinotecan-based combinations in gemcitabine-resistant pancreatic cancer haven shown conflicting results. Promising results have been reported with the combination of irinotecan and raltitrexed, irinotecan and oxaliplatin (IROX regimen) or with the G-FLIP regimen, yielding a response rate of 10-24%, a median survival of 5.9-10.4 months and a one year OS of 23-47% (8, 15, 42). Conversely, the association of mitomycin, docetaxel and irinotecan (MDI regimen) has been demonstrated to be inactive as salvage therapy with a median PFS and OS of 1.7 and 6.1 months, respectively (43). Also a fluoropyrimidine and irinotecan combination failed to obtain a survival improvement in this setting of patients. In fact similar negative results were reported in a phase II randomized trial comparing FOLFOX with FOLFIRI.3 regimen as a second-line therapy achieving a median PFS of 8.3 weeks and OS of 16.6 weeks without obtaining any objective response (44). A recently published retrospective multi-centric survey has reported a possible modest survival advantage for patients treated with FOLFIRI regimen as second-line therapy recording a 15% of response rate, a median time to progression of 3.7 months and a median survival of six months (45). These better results might be due to a bias in patient selection. In fact, 17% of patients in this series had stage III disease, which is associated with a better prognosis. No data of previous PFS were reported. All patients had received FOLFIRI regimen after only first-line gemcitabine-based chemotherapy.

The lack of activity observed in the current patient series might be explained tentatively with various hypotheses: the scarce activity of both drugs, as also suggested by other studies (5, 40, 41, 45), as salvage therapy in advanced pancreatic cancer. Another possible reason for unsuccessful outcome of the current patient series may be the negative selection of patients. At least two prior chemotherapy lines were received by 50% of patients. In a previous review of salvage therapy in advanced pancreatic cancer, previous PFS, age and CA19.9 basal value were identified as independent prognostic factors (18). In the current series, median age was 60 years, only 26% of patients had a previous PFS >6 months and 88% of patients had CA19.9 >ten times the upper limit of laboratory normal values.

Additionally, 97% of patients were pretreated with daily assumption of capecitabine at 1250 mg/m^2 until PD or for a maximum of 6 months (30). This seems to also suggest that a different dose-intensity and schedule of administration of capecitabine as in XELIRI regimen and the synergism of capecitabine and irinotecan were not able to overcome a possible acquired resistance to this drug. As expected from literature, the toxicity of this regimen was mild with a grade >2 neutropenia in 9% of patients, anemia and fatigue in 3% and hand-foot syndrome in 12%. In conclusion, these findings suggest that these combinations of fluoropyrimidines and irinotecan are not recommended for clinical use in patients with gemcitabine-resistant pancreatic cancer. However, better results may be achieved by increasing the dose intensity of irinotecan, perhaps using a weekly schedule of administration, since the best reported results were obtained in chemo-naïve pancreatic cancer patients with weekly administration of irinotecan at 50-100 mg/m^2 (21, 36).

To date, no standard regimen for salvage chemotherapy after gemcitabine failure has been identified. Therefore clinical trials of second-line therapy are urgently needed in pancreatic cancer in the attempt to identify promising new agents with activity that may subsequently be incorporated into therapeutic approaches to the initial management of this disease.

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