Curr Oncol Rep (2013) 15:182–189
DOI 10.1007/s11912-012-0290-4

The Role of the FOLFIRINOX Regimen for Advanced Pancreatic Cancer

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Published online: 23 January 2013

Abstract In 2010, the FOLFIRINOX regimen (bolus and infusional 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) emerged as a new option in patients with metastatic pancreatic cancer and a good performance status. However, at that time, some doubts were raised regarding safety issues. Similarly, no data on FOLFIRINOX were published in patients with unresectable/locally advanced or borderline resectable pancreatic cancer. This article presents the available experience with FOLFIRINOX outside clinical trials in metastatic and locally advanced pancreatic cancer patients. The safety of the regimen in patients with biliary stents and in previously treated patients is also described. FOLFIRINOX usage in clinical practice, including modification of the regimen (omission of bolus 5-fluorouracil; FOLFOXIRI regimen), is also presented. These data suggest that a phase III randomized study is warranted to further explore the role of FOLFIRINOX in locally advanced pancreatic cancer.

Keywords Pancreatic cancer · Chemotherapy · Oxaliplatin · Irinotecan

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Introduction

Pancreatic adenocarcinoma was the seventh leading cause of death from cancer worldwide in 2008 [1] and the fourth leading cause of cancer death in the USA in 2011 [2]. Pancreatic cancer still carries a dismal prognosis, with a 5-year survival rate of 6 % [2, 3]. Up to 85 % of patients are diagnosed at a stage when the tumor is unresectable because of extension to regional arteries or distant metastases are present [4, 5]. Gemcitabine has been the standard chemotherapy used in recent years, with a small randomized trial suggesting a small survival advantage over 5-fluorouracil (5-FU) chemotherapy, with better median survival (5.6 versus 4.4 months; p=0.0025) [6]. This trial also evaluated the impact of gemcitabine on "clinical benefit response," with an increase in clinical benefit responses in favor of gemcitabine (24 % versus 5 %; p=0.0022). Single-agent gemcitabine in randomized trials has consistently achieved median overall survival of 6 months and a 1-year overall survival rate of 20 % in patients with advanced pancreatic carcinoma [7]. Thirteen randomized studies comparing gemcitabine with gemcitabine plus another chemotherapeutic agent (fluoropyrimidine, cisplatin, irinotecan, oxaliplatin, pemetrexed, exatecan) have been performed and have shown no quality-of-life or survival advantage for the doublet combination. However, a large phase III trial comparing gemcitabine with the combination of capecitabine plus gemcitabine has shown an increase of

response rate (19.1 % versus 12.4 %; p=0.034) and a longer progression-free survival (PFS), without a significant effect on overall survival [8••]. However, a statistically significant benefit with regard to overall survival with this doublet combination was shown in a meta-analysis including one randomized phase II trial and two phase III trials investigating the same regimen [8••].

Of 12 randomized phase III trials using targeted agents with gemcitabine, only one succeeded in demonstrating a survival advantage for the combination. This trial compared the combination of erlotinib and gemcitabine with gemcitabine plus placebo in 569 patients with advanced pancreatic carcinoma [9]. Toxicity in the gemcitabine plus erlotinib arm was higher, resulting in rash, diarrhea, and some cases of severe interstitial lung disease. Although significant, the magnitude of median survival improvement was subtle, being 0.33 months (6.24 versus 5.91 months).

Development of the FOLFIRINOX Regimen: Phase I and Phase II Studies

The triple combination of 5-FU, irinotecan, and oxaliplatin was initially developed for treatment of metastatic colorectal cancer. The different mechanisms of action of the three drugs and their nonoverlapping toxicities provided the rationale for the study [10]. Synergism between oxaliplatin and 5-FU and between irinotecan and 5-FU was the basis for the FOLFOX and FOLFIRI regimens, respectively, which are used in several gastrointestinal malignancies. Oxaliplatin and SN-38, the main active metabolite of irinotecan, showed synergistic activity in vitro, delaying the reversion of oxaliplatin-induced DNA interstrand cross-links [11]. More cytotoxicity was found in vitro when oxaliplatin was given before SN-38. Among the six patients with metastatic pancreatic cancer enrolled in the phase I study, one patient achieved a complete response and another patient achieved a partial response. Other responses have been observed in patients with colorectal cancer, cholangiocarcinoma, and gastric carcinoma.

These encouraging data prompted us to evaluate this regimen in single-arm phase II studies in metastatic colorectal cancer [12] and pancreatic cancer [13]. Entry to the pancreatic study was restricted to patients with WHO performance status 0 or 1 given one previous trial suggested a possible benefit from combination chemotherapy was limited to patients with a Karnofsky score of 90 or 100 [14]. This was subsequently confirmed in a meta-analysis [15]. Forty-six chemotherapy-naïve patients with histologically proven advanced pancreatic adenocarcinoma were included. Eligible patients were required to have an age below 70 years, total bilirubin level 1.5 times or less than the upper limit of normal, and surgical unresectability. Eleven patients had a locally advanced disease and 35 patients had metastatic disease. All computed tomography scans were reviewed by an external response review committee. Twelve partial responses [26 %; 95 % confidence interval (CI), 13–39 %] were observed. The median response duration was 10.4 months and the median PFS was 5.6 months (95 % CI, 5.3–11.6 months). The median overall survival was 9.5 months (95 % CI, 5.6–13.7 months) in patients with metastatic disease and 15.7 months (95 % CI, 8.9–43 months) in patients with locally advanced disease. No toxic deaths occurred. Grade 3–4 neutropenia and diarrhea developed in 52 % of patients and 17 % of patients, respectively. Compliance in quality-of-life evaluation was fair (65.8 %) and only 36 patients completed both the baseline and the end-of-treatment questionnaires. Quality of life was improved for all functional scales except cognitive functioning. Responders had a 25-point improvement in other global quality-of-life scores, a major improvement according to the criteria of Osoba et al. [16].

The Phase III PRODIGE 4/ACCORD 11 Study in Metastatic Pancreatic Cancer

The promising activity of the FOLFIRINOX regimen in patients with good performance status prompted us to develop a French randomized phase II/III study comparing FOLFIRINOX with gemcitabine in patients with metastatic pancreatic cancer [17••]. Locally advanced pancreatic carcinoma (LAPC) patients were excluded, owing to both the difficulty of tumor response assessment of the primary tumor and data from previous phase III studies indicating differing outcomes with combination chemotherapy between locally advanced and metastatic disease, suggesting separation of these different populations in different trials [9, 18].

The main eligibility criteria included histologically confirmed ductal adenocarcinoma of the pancreas, measurable metastatic disease, no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, age less than 76 years, no ischemic cardiac disease within 1 year before entry, and a total bilirubin level less than 1.5 times the upper limit of normal. Patients were stratified by center, performance status (0 versus 1) and location of the primary tumor (head versus body/tail). The FOLFIRINOX regimen included oxaliplatin (85 mg/m^2) over 2 h, then irinotecan (180 mg/m^2) over 90 min concurrently with leucovorin (400 mg/m^2) over 2 h immediately following

oxaliplatin, bolus 5-FU (400 mg/m^2) and continuous intravenous infusion of 5-FU over 46 h (1,200 mg/m^2 per day for 2 days). Each cycle of therapy was repeated every 14 days. Standard supportive care was used (antiemetics, antidiarrheals, atropine in the case of cholinergic reaction to irinotecan, and patient education regarding side effects). Gemcitabine was infused at a dose of 1,000 mg/m^2 over 30 min weekly for 7 of 8 weeks, then weekly for 3 of 4 weeks. Six months of treatment was recommended for responding patients. Patients were randomly assigned to treatment with either FOLFIRINOX or gemcitabine. Granulocyte colony-stimulating factor (G-CSF) was not allowed as primary prophylaxis. Computed tomography scans were obtained every 2 months. The response rate was the primary end point of the phase II portion of the study, which was planned to continue as a phase III study if at least 12 objective responses occurred in the first 44 patients in the FOLFIRINOX group. Response evaluation criteria in solid tumors (RECIST) were used for response assessment, and an external review committee reviewed all the responses of randomized phase II patients. Quality of life was measured by EORTC QLQ-C30 questionnaires at the baseline, then every 2 weeks. The study was designed to have 80 % power to detect an increase in median overall survival from 7 to 10 months [hazard ratio (HR) 0.70, α=0.05]. Three hundred and sixty patients were required to reach 250 events for final analysis. At the planned interim analysis after 167 events, the independent data monitoring committee recommended stopping the accrual because the primary end point was met with a p value of less than 0.001.

Between January 2005 and October 2009, 342 patients were enrolled at 48 French centers. Patient characteristics were balanced between the arms for age, gender, baseline performance status, location of primary disease, timing of metastases, median number of involved sites, baseline cancer antigen (CA) 19–9 level, biliary stents, and metastatic sites, except for a greater percentage of measurable lung metastases in the gemcitabine arm (28.7 % versus 19.5 %; p<0.005). The median age was 61 years. Approximately 38 % of patients had tumors of the pancreatic head, with a biliary stent in 14 % of patients. The median number of treatment cycles (one cycle corresponded to 14 days) was ten in the FOLFIRINOX arm (range 1–47) and six in the gemcitabine arm (range 1–26).

In the randomized phase II portion, the response rate according to the investigator in the FOLFIRINOX arm was 14/44 (31.8 %), and was 15/44 (34 %) according to an independent radiologic review. Similarly, in the phase III portion, the final objective response rate was 31.6 % (95 % CI, 24.7–39.1) in the FOLFIRINOX arm and 9.4 % (95 % CI, 5.4–14.7) in the gemcitabine arm (p<0.0001). The disease control rate (stable disease plus objective responses) was 70.2 % in the FOLFIRINOX arm versus 50.9 % in the gemcitabine arm (p=0.0003). The median duration of response was not significantly different, 5.9 versus 4 months in the FOLFIRINOX and gemcitabine arms, respectively.

Not surprisingly, patients who received FOLFIRINOX experienced significantly higher rates of grade 3–4 neutropenia (45.7 % versus 21 %), febrile neutropenia (5.4 % versus 1.2 %), thrombocytopenia (9.1 % versus 3.6 %), diarrhea (11.4 % versus 1.2 %), and peripheral neuropathy (9 % versus 0 %) than those who received gemcitabine. One toxic death occurred in each arm. The risk of infection and of hematologic toxicities was similar with or without a biliary stent in the FOLFIRINOX arm. A trend for more grade 3–4 infection was observed in patients with a stent in the gemcitabine arm (9.5 % versus 2 %; p=0.058).

Patients on the FOLFIRINOX regimen also achieved a longer PFS (5.4 versus 3.3 months; HR=0.47; 95 % CI, 0.37–0.59; p<0.0001). Median overall survival was significantly longer with the multidrug regimen (11.1 months versus 6.8 months; HR=0.57; 95 % CI, 0.45–0.73; p< 0.0001). The 1-year survival rate was 48.4 % versus 20.6 % in the FOLFIRINOX and gemcitabine arms, respectively. Survival from second-line therapy was 4.4 months in both arms. The benefit of FOLFIRINOX was observed in all patients subgroups.

Quality of life was similar between treatment arms at all times for EORTC QLQ-C30 domains, with the exception of diarrhea, which appeared to be negatively affected in the FOLFIRINOX arms during the first 2 months of treatment. Quality of life improved in both groups [19•]. However, the time until definitive deterioration in quality of life was significantly longer in the FOLFIRINOX arms for all EORTC QLQ-C30 domains, except insomnia, diarrhea, and financial difficulties [17••]. In the multifactorial analysis, gemcitabine delivery, age greater than 65 years, low serum albumin level, synchronous metastases, and hepatic metastases had a negative impact on overall survival. On the basis of these data, FOLFIRINOX is the only combination regimen to date with a clinically significant survival benefit over gemcitabine in patients with good performance status.

FOLFIRINOX Results in Routine Practice

The phase III results had an impact on clinical practice beginning 1 month after presentation at the 2010 American Society of Clinical Oncology meeting. American medical oncologists (n=372) were asked about their preferences, and

18 % planned to prescribe FOLFIRINOX in metastatic patients with performance status 1 [20]. Moreover, according to Canadian researchers, FOLFIRINOX is cost-effective. These investigators conducted a medicoeconomic analysis of first-line FOLFIRINOX therapy followed by second-line gemcitabine therapy compared with first-line gemcitabine therapy followed by second-line chemotherapy. Whatever the choice of treatment after gemcitabine therapy (platinum-based regimen or supportive care), in this analysis, using FOLFIRINOX as first-line treatment added more overall life-years and quality-adjusted life-years when compared with first-line gemcitabine therapy [21].

Some concerns have been raised regarding possible differing toxicity profiles of FOLFIRINOX in non-French populations [22], owing to variability of the metabolism of fluoropyrimidines around the world. Multiple retrospective and prospective heterogeneous series have now confirmed the similar efficacy and toxicity profiles in European and US populations outside the clinical trial setting. No results from Asian trials are available to our knowledge. A multi-institutional experience of FOLFIRINOX was recently published [23] using a retrospective and prospective registry. A total of 61 patients were enrolled. The median age was 58 years, and 31 % of patients had LAPC. Eight patients (13 %) had ECOG performance status 2 or unknown status. The FOLFIRINOX regimen was modified in 50.8 % of patients starting with the first cycle, because of concern for potential toxicities. Deletion of bolus 5-FU and dose reduction of irinotecan, owing to the presence of the UGT A1*28/28 genotype, were the commonest modifications. No toxic deaths occurred. Prophylactic G-CSF support was used in 67 % of patients. Grade 3–4 neutropenia occurred in 19.7 % of patients, including a febrile neutropenia rate of 4.9 %, similar to that in the French trial. Forty patients were evaluable, with an overall response rate of 25 %, with a stable disease rate of 47 %. Patients with borderline resectable disease underwent subsequent resection, as did four of 19 patients with LAPC. Prophylactic G-CSF administration did not significantly change the rate of grade 3–4 neutropenia (3.2 % versus 4.6 %), but patients receiving G-CSF experienced significantly more anemia and thrombocytopenia. As in the pivotal phase III study, no differences in grade 3–4 toxicities according to the presence/absence of a biliary stent were observed. A good safety profile of the regimen when it was given to patients with biliary stents was also observed in another series [24].

In a retrospective analysis of a US multi-institutional experience with FOLFIRINOX in 54 patients [25], partial response was documented in 39 % of patients and the median overall survival was only 7.2 months, possibly partly due to treatment of patients with poor performance status (9 % of patients had performance status greater than 1). Side effects, mainly vomiting, febrile neutropenia, and fatigue, led to discontinuation of treatment in a third of the population. There were no toxic deaths.

Conversely, Massachusetts General Hospital investigators treated 29 patients with FOLFIRINOX, including 41 % of patients with LAPC [26]. Eleven patients received prior chemotherapy. Overall, 11 partial responses were observed (38 %); all responses except one were observed in chemotherapy-naïve patients. Four patients (13.7 %) had febrile neutropenia. Response rates were similar in patients with metastatic disease and LAPC (35 % and 42 %, respectively).

However, further data from the USA and Europe [24, 27, 28•, 29] confirmed the response rate previously described in the phase III study. Whether future targeted therapies will be able to be combined with FOLFIRINOX remains to be investigated. Presently, only one phase Ib trial of FOLFIRINOX plus saridegib has been presented with concurrent FOLFIRINOX, omitting the 5-FU bolus [30].

In the ACCORD 11 study, 32 % of the patients did not receive bolus 5-FU after one to four cycles. The response rate was not significantly different in patients who received bolus 5-FU through the fourth cycle versus those in whom bolus 5-FU was stopped during the first four cycles (34.8 % versus 25.8 %).

As bolus 5-FU contributes to the hematologic toxicity of the regimen, investigators from Emory University treated 60 patients with modified FOLFIRINOX with deletion of the 5-FU bolus and administration of prophylactic pegfilgrastim in all patients [31]. The incidence of grade 3–4 neutropenia was 3 %. Thirty-six patients (60 %) had metastatic disease, 20 patients (34 %) had unresectable LAPC, and two patients had stage II/borderline resectable disease. Fifty patients were evaluable for response: the overall response rate was 30 % (95 % CI, 0.18–0.45), including two complete responses. Twenty-seven patients (54 %) had stable disease. Despite omission of bolus 5-FU, most patients achieved disease control with FOLFIRINOX.

Memorial Sloan-Kettering Cancer Center physicians treated 80 patients with FOLFIRINOX as first-line therapy [29]. The median starting dose of FOLFIRINOX was 80 % of that used in the ACCORD 11 trial, and 82 % of patients received prophylactic growth factor. Despite these dose reductions, the efficacy was maintained, with 21 of 61 patients (40 %) achieving a partial response in a metastatic setting and a four of 19 patients (21 %) with LAPC achieving a partial response.

A retrospective review was also performed by investigators at Yale University [27]. Thirty-one patients with a median age of 60 years were treated with FOLFIRINOX;

48 % had LAPC and five patients had had chemotherapy. Only five patients received full doses of all drugs in cycle 1, with median relative doses of oxaliplatin, irinotecan, bolus 5-FU, and infusional 5-FU of 88 %, 64 %, 57 %, and 100 %, respectively (a lower dose intensity than in the ACCORD 11 trial). Despite dose modifications, the response rate was 33 % in 30 evaluable patients, including one complete response. Two patients with LAPC underwent resection.

Other modifications of FOLFIRINOX have been proposed, including FOLFOXIRI, a regimen which differs from FOLFIRINOX in a lower dose of irinotecan (150 mg/m^2), omission of bolus 5-FU, and high dose of infusional 5-FU (2,800 mg/m^2 in 48 h). In a report from Pisa University, 22 patients with LAPC were treated with FOLFOXIRI. Among 15 evaluable patients, six partial responses (40 %) and nine patients with stable disease (60 %) were observed [32], with a median PFS of 24.5 months. The same investigators also treated 39 patients with advanced pancreatic adenocarcinoma with the FOLFOXIRI regimen [33]. Among 30 evaluable patients, 11 partial responses (36.7 %) were observed. The median PFS was 11.5 months and the median overall survival 25.5 months. For metastatic patients only, the response rate was 33 %, with a PFS and an overall survival of 8.4 and 14.8 months, respectively. No toxic deaths or febrile neutropenia occurred.

Two retrospective series evaluated the efficacy and toxicity of FOLFIRINOX as second-line therapy after first-line chemotherapy with gemcitabine [34, 35] in 27 and 13 patients, respectively. The response rate was 19 % (5/22) in one study and 0 % in the other one, although six stable disease outcomes (in nine patients) were observed. Median overall survival was 8.5 and 13.3 months, respectively. Another study included ten patients with performance status 2–3, although no details were given on toxicities and response rates [34]. A favorable tolerance profile and efficacy of the FOLFIRINOX regimen in this population of frailer patients was confirmed.

Use of FOLFIRINOX in LAPC: Preliminary Data

Up to 40 % of patients with newly diagnosed pancreatic cancer present with locally advanced, unresectable disease because of vascular encasement. These patients were excluded from the pivotal phase III FOLFIRINOX trial. Many patients with LAPC have occult metastases and will present early on with metastatic progression, emphasizing the importance of more effective systemic therapies. In a routine setting, during multidisciplinary team meetings, pancreatic surgeons will distinguish borderline resectable pancreatic cancer from truly unresectable pancreatic cancer. Consensus criteria have been recently published to clearly define borderline resectable tumors and definitively unresectable cancers [36]. In definitively unresectable pancreatic cancer, many options have been proposed: chemotherapy alone, concomitant chemoradiotherapy, or both. Retrospective data suggested that induction chemotherapy followed by chemoradiotherapy may identify patients with early metastatic progression who would not benefit from aggressive chemoradiotherapy [37]. Some retrospective and prospective series have suggested that the FOLFIRINOX combination therapy is active in LAPC (Table 1). In some patients,

Table 1 FOLFIRINOX (bolus and infusional 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) for patients with locally advanced pancreatic cancer

Authors	No. of patients	Regimen	Response rate	No. of patients with resection	R0 resections	Median survival (months)
Conroy et al. [13]	11	FOLFIRINOX	3/11 (27 %)	0	0	15.7
Mahaseth et al. [31]	20	FOLFIRINOX, then chemoradiotherapy (10 patients)	Not stated	4	3	17.8
Peddi et al. [23]	19	FOLFIRINOX + G-CSF (77 %)	6/18 (33 %)	4 of 19 (21 %)	-	Not reached
Marthey et al. [39]	77	FOLFIRINOX (62 % of patients)	22/77 (28.6 %)	28 (36 %)	Not stated	Not reached
Vasile et al. [32]	15	FOLFIRINOX, then chemoradiotherapy (3 patients) or surgery (6 patients)	6/15 (40 %)	5 of 6	-	30.1
Lowery et al. [29]	19	FOLFIRINOX (80 % dose)	4/19 (21 %)	-	-	13.7
Gunturu et al. [27]	15	FOLFIRINOX + pegfilgrastim	Not stated	2	-	-
Faris et al. [26]	12	FOLFIRINOX	5/12 (42 %)	1	-	-
Hosein et al. [28•]	25	FOLFIRINOX, then chemoradiotherapy (9 patients)	Not stated	4 after CT, 3 after CRT	5	Not reached

G-CSF granulocyte colony-stimulating factor, *CT* computed tomography, *CRT* chemoradiotherapy

Table 2 FOLFIRINOX for patients with borderline resectable pancreatic cancer

Authors	No. of patients	Regimen	No. of patients with resection	R0 resections	Median survival
Mahaseth et al. [31]	2	FOLFIRINOX, then chemoradiotherapy	2 of 2	2	Not stated
Kharofa et al. [38]	12	FOLFIRINOX (4 cycles), then chemoradiotherapy with gemcitabine	7 of 12	7	Not reached at 13 months
Peddi et al. [23]	4	FOLFIRINOX	4 of 4	Not stated	Not stated
Hosein et al. [28•]	4	FOLFIRINOX (6–17 cycles)	3 of 4	3	Not stated

downsizing of the tumor has been achieved, leading to R0 resection [23, 28•, 31, 38].

In a French prospective study of 77 patients with LAPC treated with the FOLFIRINOX regimen in 11 French hospitals, FOLFIRINOX seems to be feasible with a manageable toxicity profile [39]. Unresectability was determined by a local multidisciplinary team meeting. The median number of cycles was five (1–30). No toxic deaths occurred. The rate of grade 3–4 toxicities was 26 %, and only 6 % of patients had to stop treatment because of toxicities. In 77 evaluable patients, the partial response rate was 28.6 %. Twenty-eight patients (36 %) had secondary surgical resection. The 1-year survival rate was 77 % and the 1-year PFS rate was 59 %. These encouraging results suggested that a phase III study should be conducted.

The feasibility of FOLFIRINOX as neoadjuvant chemotherapy has been described in a retrospective analysis at Miami University [28•]. Eighteen patients assessed as having unresectable LAPC (14 patients) or borderline resectable LAPC (four patients) received FOLFIRINOX. A median of eight cycles (range 3–17) per patient was administered. Among 14 patients with initially unresectable cancer, four patients had potentially resectable tumor after treatment with FOLFIRINOX, and two R0 resections and one R1 resection were performed. Nine patients had tumors that were still unresectable and went on to receive chemoradiotherapy. Three of the tumors were converted to potentially resectable tumors and three R0 resections were performed. Among the four patients with borderline resectable disease, three patients had R0 resection after six to 17 cycles of FOLFIRINOX therapy. Overall, seven patients (39 %) were converted to resectability by radiologic criteria and six had R0–R1 resection. After chemoradiotherapy, 44 % of patients (95 % CI, 22–69 %) had a R0 resection. Other experiences in small numbers of patients have been published in abstract form (Table 2) These promising results have to be confirmed by an ongoing multi-institutional US Alliance Intergroup study of modified FOLFIRINOX therapy followed by chemoradiotherapy (A021101 phase II study).

Future Directions

In addition to the Alliance study, the FOLFIRINOX regimen will be prospectively evaluated by the PRODIGE group in LAPC patients, in comparison with treatment with gemcitabine, both followed by chemoradiotherapy. FOLFIRINOX is now being tested as adjuvant chemotherapy in the French-Canadian PRODIGE 24-ACCORD 24/0610. In this ongoing study, there is omission of bolus 5-FU without any other changes of the regimen (modified FOLFIRINOX). Patients with performance status 0–1, age less than 80 years, and postoperative CA 19–9 level less than 180 U/ml are eligible. Patients will be stratified by center, surgical margins (R0 versus R1), node status (pN0 versus pN1) and postoperative CA 19–9 level (90 U/ml or less versus 91–180 U/ml). Patients are randomized to 24 weeks of gemcitabine therapy or 12 cycles of modified FOLFIRINOX therapy. The study requires 490 patients to demonstrate a 10 % increase in disease-free survival at 3 years.

Conclusion

After 20 years of disappointing results in advanced pancreatic cancer, FOLFIRINOX is now the reference treatment in patients with good performance status and is cost-effective. Gemcitabine is still a reasonable option in patients with poor performance status or contraindication to FOLFIRINOX. Some data have suggested activity of FOLFIRINOX in previously treated patients. Retrospective and prospective series have confirmed the significant activity of FOLFIRINOX in metastatic pancreatic cancer as well as in LAPC. Further investigation is needed to continue improving survival outcomes in these patients with identification of predictive biomarkers and to develop further combination or maintenance therapeutic strategies.

Disclosure T. Conroy: none; C. Gavoille: none; E. Samalin: none; M. Ychou: none; and M. Ducreux: board membership (Sanofi) and honoraria (Sanofi and Pfizer).

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