A New Direction for Pancreatic Cancer Treatment: FOLFIRINOX in Context

By Hedy Lee Kindler, MD

Overview: Since 1996, the cornerstone of chemotherapy for advanced pancreatic cancer has been gemcitabine, which has a genuine, but modest effect on survival and quality of life. It has been remarkably difficult to improve on these outcomes. Many phase III studies of gemcitabine doublets have been uniformly negative, with the exception of a trial of gemcitabine plus erlotinib, which provided only marginal benefit. In 2010, the FOLFIRINOX regimen (bolus and infusional 5-fluorouracil, irinotecan, and oxaliplatin) emerged as a major treatment advance for patients with metastatic pancreatic cancer. In a trial with 342 patients, FOLFIRINOX yielded a longer median overall survival (11.1 vs. 6.8 months, hazard ratio [HR] 0.57, \( p < 0.001 \)), a superior progression-free survival (6.4 vs. 3.3 months, HR 0.67, \( p < 0.001 \)), a higher objective response rate (31.6% vs. 9.4%, \( p < 0.001 \)), and a significant increase in time until definitive deterioration in quality of life, compared with gemcitabine. FOLFIRINOX is also more cost-effective than gemcitabine. Because of higher rates of grade 3 to 4 neutropenia (46% vs. 21%), febrile neutropenia (5% vs. 1%), and diarrhea (13% vs. 2%) with FOLFIRINOX, vigilant patient selection, education, and monitoring are essential. Retrospective single-institution series confirm the substantial activity of FOLFIRINOX in metastatic, locally advanced, and previously-treated patients; demonstrate its safety in individuals with biliary stents; and elucidate how physicians routinely modify drug doses without clear evidence or guidelines. Ongoing and planned studies will prospectively evaluate FOLFIRINOX in the adjuvant, locally advanced, and borderline resectable settings, will add targeted agents to FOLFIRINOX, and will evaluate how to adjust doses to ameliorate toxicity.

Background

THERE HAS been a long-standing, well-deserved therapeutic nihilism regarding chemotherapy for advanced pancreatic cancer. In countless trials over the past few decades, many drugs and drug combinations have demonstrated minimal to no activity against this devastating disease.

Since 1996, the cornerstone of therapy has been gemcitabine, an agent with a genuine, but modest impact. In the pivotal trial that compared gemcitabine to weekly bolus 5-fluorouracil (5-FU), gemcitabine treatment yielded a response rate of 5% and a median overall survival of 5.7 months.\(^1\) Although these results do represent a real advance over 5-FU, gemcitabine is principally given because it provides a clinical benefit, a combination of an improvement of pain and performance status, and a stabilization of weight.

Despite these very modest outcomes, it has been difficult for any agent to displace gemcitabine for advanced pancreatic cancer. Most drugs simply do not work in this disease. Although innumerable phase II trials have reported “promising activity” for various gemcitabine-based cytotoxic and targeted doublets, phase III trials of these combinations have been uniformly disappointing, generally yielding greater toxicity for the multidrug regimens with no improvement in overall survival.\(^2-7\)

This dismal outlook changed slightly in 2005, when the National Cancer Institute of Canada PA.3 trial demonstrated a small improvement in survival for patients treated with gemcitabine plus erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor.\(^8\) Although the results were statistically significant, with a hazard ratio of 0.82, the absolute improvement in median overall survival, 5.91 months with gemcitabine compared with 6.24 months for gemcitabine/erlotinib, was minimal. This combination also came with a substantial economic cost\(^9\) and did not improve quality of life. One could easily question whether such an incremental improvement in overall survival was worth the expense and toxicity.\(^10\) Over the next 5 years, several more negative phase III trials were reported,\(^11-16\) and it certainly appeared that any major improvements were a long way off.

It was in this context that the results of the PRODIGE 4/ACCORD 11 trial, presented first at ASCO in 2010\(^17\) and published in the New England Journal of Medicine in 2011,\(^18\) represent a substantial treatment advance for patients with pancreatic cancer. The multidrug combination FOLFIRINOX significantly improved median and progression-free survival, objective response rates, and quality of life, albeit with greater toxicity. Given all of the negative trials that preceded it, these data alone are a major achievement. What is truly unprecedented is the magnitude of the benefit achieved with this regimen.

In this article, we will review the data behind this pivotal study, examine how oncologists are currently using this regimen, and assess the ways that FOLFIRINOX may be incorporated into pancreatic cancer treatment in the future.

Development of the FOLFIRINOX Regimen: Phase I and II Studies

It would seem logical to combine 5-FU, irinotecan, and oxaliplatin: these 3 drugs have activity in several gastrointestinal malignancies, including pancreatic cancer, without many overlapping toxicities. The doses for the FOLFIRINOX regimen were established in a phase I trial of 34 evaluable patients with advanced solid tumors enrolled between 1998 and 2000.\(^19\) Although the investigators may have been primarily interested in developing this combination for metastatic colon cancer, they also observed two responses (one complete and one partial) among the six patients with pancreatic cancer enrolled on the study.

These encouraging data prompted the same investigators to evaluate this regimen in a single-arm phase II trial.\(^20\) Forty-six chemotherapy-naïve patients with pancreatic cancer with a World Health Organization (WHO) performance status of 0 or 1 enrolled at nine French centers from 2000 to 2002. Most subjects (76%) had metastatic disease, a perfor-
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The impressive activity observed with FOLFIRINOX in the phase I and II trials\textsuperscript{19,20} prompted the development of a randomized phase II/III study that compared this new regimen with the benchmark therapy, gemcitabine.\textsuperscript{18} Key eligibility criteria included no prior chemotherapy, an ECOG Performance Status of 0 or 1, age less than 76 years, measurable metastatic disease, and a total bilirubin less than 1.5 times the upper limit of normal.

Patients, stratified by center, performance status (0 vs. 1), and location of the primary tumor (head vs. body/tail) were randomized 1:1 to either FOLFIRINOX (oxaliplatin 85 mg/m\textsuperscript{2}, leucovorin 400 mg/m\textsuperscript{2}, irinotecan 180 mg/m\textsuperscript{2}, bolus 5-fluorouracil 400 mg/m\textsuperscript{2} followed by infusional 5-fluorouracil 2,400 mg/m\textsuperscript{2} given over 46 hours, every 14 days) or gemcitabine (1,000 mg/m\textsuperscript{2} over 30 minutes weekly for 7 of 8 weeks, then weekly for 3 of 4 weeks). Each cycle was defined as a 2-week interval for both regimens. Six months of treatment were recommended for responding patients. Filgrastim was not routinely administered for primary prophylaxis, though it was permitted for high-risk patients. Computed tomography (CT) scans were obtained every 2 months. RECIST criteria were employed for response assessment.\textsuperscript{22} Quality of life was measured by EORTC QLQ-C30 questionnaires completed every 2 weeks.

Response was the primary efficacy endpoint of the phase II portion of the study, which was planned to proceed to phase III if at least 12 objective responses occurred in the first 40 FOLFIRINOX-treated patients. Overall survival was the primary phase III endpoint. Phase II patients were included in the phase III analysis.

The study was designed to have an 80% power to detect an increase in median overall survival from 7 to 10 months (HR 0.70, \(p = 0.05\)). For the final analysis, 360 patients would be required to reach 250 events; an interim analysis was planned after 167 events occurred.\textsuperscript{23} In September 2009, the Independent Data Management Committee recommended that accrual be stopped early, because a planned interim analysis determined that the primary endpoint was achieved with a \(p\) value of less than 0.001.\textsuperscript{18,23}

Between 2005 and 2009, 342 patients enrolled at 48 French centers. Patient characteristics were balanced between the arms for age, sex, performance status, tumor location, biliary stenting, metastatic sites, and baseline Ca 19–9 level, except that a greater percentage of patients on the gemcitabine arm had measurable pulmonary metastases (29\% vs. 19\%). The median age was 61. Approximately 60\% of the subjects in both arms had a PS of 1, and approximately 87\% had liver metastases. Only 38\% of patients had tumors of the pancreatic head, and only 14\% had a biliary stent.

The median number of 2-week treatment cycles was 10 in the FOLFIRINOX arm and 6 in the gemcitabine arm (\(p < 0.001\)). The median relative dose intensity was approximately 80\% for each of the component drugs in the FOLFIRINOX regimen and 100\% for gemcitabine.

Independent radiologic review confirmed that 15 of the first 44 FOLFIRINOX-treated patients (34\%) in the phase II portion of the trial had an objective response, meeting the criteria for the study to proceed to phase III. Patients treated with FOLFIRINOX achieved a much higher objective response rate (31.6\%) than those who received single-agent gemcitabine (9.4\%).

Median overall survival was significantly longer in the patients treated with FOLFIRINOX (11.1 months vs. 6.8 months, HR = 0.57, 95\% CI, 0.45 to 0.73; \(p < 0.001\)). Overall survival rates at 6, 12, and 18 months were also superior for FOLFIRINOX-treated patients (76\%, 48\%, and 19\% respectively), compared with 58\%, 21\%, and 6\%, respectively for those who received gemcitabine. Patients on the multidrug regimen also achieved a superior progression-free survival (6.4 months vs. 3.3 months, HR = 0.47; 95\% CI, 0.37 to 0.59; \(p < 0.001\)). The beneficial effect of FOLFIRINOX was similar in all patient subgroups. These data are summarized in Table 1.
Patients who received FOLFIRINOX experienced significantly higher rates of grade 3 and 4 neutropenia (46% vs. 21%), febrile neutropenia (5% vs. 1%), thrombocytopenia (9% vs. 4%), and sensory neuropathy (9% vs. 0%) than those who received gemcitabine. The presence of a biliary stent did not increase the risk of infection in either arm, and no cholangitis was reported. Filgrastim was given to 43% of FOLFIRINOX-treated patients. Toxicity data are summarized in Table 2.

Significantly more patients on the gemcitabine arm had a definitive decrease in their scores on the Global Health Status and Quality of Life scale compared with those on the FOLFIRINOX arm (66% vs. 31%, HR = 0.47, p < 0.001). A significant increase in the time until definitive deterioration in quality of life was observed in the FOLFIRINOX-treated subjects for all functional and symptom scales.

FOLFIRINOX Usage in Clinical Practice

Almost immediately after Conroy presented the FOLFIRINOX data at ASCO in 2010, Xcenda, LLC analyzed the prescribing plans of American oncologists using the NMCR Challenging Cases live research vehicle.24 From July 31 to August 28, 2010, they assessed the prescribing plans of more than 370 U.S. oncologists for first-line therapy of patients with metastatic pancreatic cancer and PS 1 or 2. They observed that the FOLFIRINOX data produced an immediate change in the distribution of planned first-line prescribing. For the PS 1 scenario, FOLFIRINOX had an 18% share; in the previous year, those patients would mostly have received gemcitabine/erlotinib. As expected, plans for FOLFOX in the previous year, those patients would mostly have received gemcitabine/erlotinib. As expected, plans for FOLFOX in the previous year, those patients would mostly have received gemcitabine/erlotinib. 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tients with pancreatic cancer who were treated with FOLFIRINOX at their institution between June 2010 and June 2011, and compared patient characteristics, toxicities, and response rates with those reported in the pivotal phase III trial.\(^1\) Thirty-five patients, with a median age of 61, were treated with FOLFIRINOX; 68% had an ECOG PS of 0, 57% had pancreatic head tumors, 46% had locally advanced disease, and only 14% had received prior chemotherap\(\text{y}\).

Only 17% of patients received full-dose FOLFIRINOX with the first cycle. Irinotecan was reduced in 93% of patients and omitted in 3%; oxaliplatin was reduced in 34%; bolus 5-FU was reduced in 31% and omitted in 24%; leucovorin was decreased in 37%; and the 5-FU continuous infusion was decreased in 10%. Median of 10 cycles was delivered. The median relative doses of oxaliplatin, irinotecan, bolus 5-FU, and infusional 5-FU were 90%, 68%, 68%, and 100%, respectively (in the phase III trial the median relative doses of oxaliplatin, irinotecan, and 5-FU [bolus and infusion] were 78%, 81%, and 82%, respectively). Yale patients experienced significantly less grade 3/4 fatigue (\(p = 0.0089\)) and neutropenia (\(p < 0.0001\)) compared with patients in the phase III trial. Despite routine dose modifications, the response rate, progression-free survival, and overall survival were not significantly different from historic controls. The authors concluded that modest dose attenuations of FOLFIRINOX reduce toxicity but do not appear to compromise its efficacy.

The activity of FOLFIRINOX in previously treated patients has been described in two retrospective series from France.\(^2\) In a retrospective review of 27 patients who received second-line FOLFIRINOX from 2003 to 2009, a median of six cycles were delivered. Grades 3–4 neutropenia developed in 56%, and one patient experienced grade 5 febrile neutropenia; 44% received growth factors as second-line FOLFIRINOX from 2003 to 2009, a median of six cycles were delivered. Grades 3–4 neutropenia developed in 56%, and one patient experienced grade 5 febrile neutropenia; 44% received growth factors as second-line treatment was also included in their analysis.

Their first model, based on the ACCORD 11 trial data, assumed that in one arm patients received first-line FOLFIRINOX and second-line gemcitabine, and in the other arm, they received first-line gemcitabine and second-line platinum-based chemotherapy; in both groups G-CSF usage was allowed.

The second analysis, which mirrored current Ontario treatment patterns, assumed that first-line FOLFIRINOX was followed by second-line gemcitabine in one arm, and first-line gemcitabine was followed by best supportive care in the other arm; no G-CSF was permitted.

In both scenarios, first-line FOLFIRINOX produced more life years and quality-adjusted life years (QALY) than first-line gemcitabine. The costs per QALYs for FOLFIRINOX were about $45,000 to $55,000. Thus, even though the component drugs of the FOLFIRINOX regimen cost more than single-agent gemcitabine, FOLFIRINOX is more cost-effective than gemcitabine. FOLFIRINOX has therefore received a favorable funding recommendation in most Canadian provinces.

Future Directions with FOLFIRINOX

Given the impressive activity of FOLFIRINOX in the metastatic setting, plans are underway to prospectively evaluate this regimen in the adjuvant, locally advanced, and borderline resectable settings, studies are ongoing to add targeted agents to FOLFIRINOX, and trials are in development to determine how to adjust doses and ameliorate toxicity.

PRODIGE 24-ACCORD 24/0610 will be the first trial to evaluate FOLFIRINOX in the adjuvant setting. This study will use a modified regimen, called mFOLFIRINOX, in which the bolus 5-FU has been omitted and all other drug doses remain unchanged. Eligible patients with resected head, body, or tail lesions, PS 0–1, age less than 80 years, total bilirubin less than 1.5 X ULN, and Ca 19–9 less than 180, will be stratified by center, node status, postoperative Ca 19–9 level (90 vs. 91–180), and surgical margin (R0 vs. R1), and randomized to 24 weeks of gemcitabine or mFOLFIRINOX. The primary endpoint will be 3-year disease-free survival. A 30-patient lead-in safety analysis will soon be initiated to ascertain that the rate of grade 3–4 diarrhea is less than 5%. The study requires 490 patients to demonstrate a 10% increase in disease-free survival at 3 years, from 17% to 27%. It will be conducted in France and Canada.

The safety of FOLFIRINOX in borderline resectable patients has been described in a retrospective series.\(^3\) A021101 is a 50-patient, single-arm, neoadjuvant phase II U.S. Intergroup study of mFOLFIRINOX followed by chemoradiation then surgery and postoperative gemcitabine for patients with borderline resectable pancreatic cancer. This benchmark trial will assess the feasibility of a multi-institutional effort in this patient subgroup and provide a foundation for future trials. The primary endpoint is 1-year overall survival.

FOLFIRINOX may also serve as a platform for the addition of targeted agents, though caution must be used because of the potential for overlapping toxicities. The Cancer and Leukemia Group B (CALGB) will be leading a phase IB/randomized phase II trial of mFOLFIRINOX plus placebo or ganitumumab (a monoclonal antibody to the insulin growth factor 1 receptor), in patients with previously untreated metastatic pancreatic cancer. This will be the first U.S. cooperative group trial to confirm the European experience with FOLFIRINOX.

A phase IB dose-finding study of FOLFIRINOX plus IPI-926, a hedgehog pathway inhibitor, is currently ongoing. Once a phase II dose is determined, this combination will be incorporated in a randomized phase II study in development in CALGB and ECOG, in which patients with locally advanced disease are randomized to FOLFIRINOX plus IPI-926 or placebo, followed by chemoradiation. A phase IB study of FOLFIRINOX plus the hedgehog inhibitor LDE225 is also accruing patients.
The Southwest Oncology Group (SWOG) is in the process of designing a randomized trial that compares FOLFIRINOX with FOLFOX, to determine whether irinotecan is an essential component of the regimen. Another approach is to ascertain which patients would be most likely to develop toxicity from irinotecan and adjust doses accordingly. UGT1A1 is the enzyme responsible for clearing SN-38, the active metabolite of irinotecan; germline polymorphisms in the UGT1A1 gene are known to reduce enzymatic activity. Thus, patients treated with FOLFIRINOX who have different UGT1A1 genotypes may tolerate different doses of irinotecan. Using genotype-guided dosing, investigators at the University of Chicago will soon open a phase I study to establish the optimal safe doses of irinotecan in the mFOLFIRINOX regimen for each of three UGT1A1 genotype groups (*1*/*1, *1*/*28, and *28/*28).

Conclusion

After so many negative randomized trials of gemcitabine doublets, the unprecedented outcomes achieved with the FOLFIRINOX regimen clearly represent a major treatment advance for those patients with pancreatic cancer who have a good performance status. No other randomized study has ever achieved a median survival of nearly a year. In no other trial have we even whispered about an 18-month survival in a proportion of patients with metastatic disease. No other phase III study has achieved such a high objective response rate. And despite substantial, though manageable toxicities, FOLFIRINOX also helps patients feel better for longer than if they received gemcitabine, a drug used principally for its effect on symptoms. Remarkably, this new drug combination is even cost-effective.

The investigators in this study are to be commended not only for the decade they spent in developing the highly active FOLFIRINOX regimen. They are also to be applauded for a very well-designed pivotal study, which tested this therapy in a uniform population of patients (all metastatic), who, with their good performance status, were most likely to tolerate the rigors of the multidrug combination and were thus most able to benefit from it.

Unanswered questions remain about the optimal way to dose the component drugs to minimize toxicity while preserving activity. Upcoming studies will address the potential role of this regimen in other disease settings and will use FOLFIRINOX as a platform on which to add new agents.

It has been a long journey, but with the advent of FOLFIRINOX, we are finally beginning to make progress against this dismal disease.

**Author’s Disclosures of Potential Conflicts of Interest**

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