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COMMENTS AND CONTROVERSIES

FOLFIRINOX: A Small Step or a Great Leap Forward?

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Clinical trials in advanced pancreatic cancer during the last couple of decades have almost uniformly yielded disappointing results. To date, the paradigm for almost all phase III studies has been to compare the long-time reference standard, gemcitabine, with a gemcitabine-based combination regimen. Agents evaluated in combination with gemcitabine have been myriad; these have included both cytotoxic drugs (platinum analogs, fluoropyrimidines, and camptothecins) and targeted therapies (inhibitors of farnesyl transferase, matrix metalloproteinase, vascular endothelial growth factor, and epidermal growth factor receptor, to name a few). With the exception of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib—which produced a modest incremental improvement when added to gemcitabine[1]—none of these individual trials demonstrated a statistically significant survival benefit in favor of doublet therapy, although some have shown improvement in secondary outcome measures such as response rate and time to tumor progression. The continued use of multidrug regimens, in fact, has been guided more by a bias in oncology practice that combination therapy is better than monotherapy, meta-analyses that indicate a survival advantage with certain combinations, particularly in patients who retain a good performance status,[2] and practice guidelines, rather than by compelling prospective randomized phase III data.

With this as background, the results of the ACCORD4/Partenariat de Recherche en Oncologie Digestive (PRODIGE) 11 trial, first presented by Conroy et al[3] at the 2010 annual meeting of the American Society of Clinical Oncology and recently published in the May 12, 2011, issue of the *New England Journal of Medicine*, are nothing short of eye opening. In this phase II/III trial conducted at 48 centers throughout France, 342 patients with previously untreated metastatic pancreatic cancer were randomly assigned to receive either gemcitabine monotherapy or a nongemcitabine-based regimen called FOLFIRINOX (biweekly bolus plus infusional fluorouracil, leucovorin, irinotecan, and oxaliplatin). There was a statistically significant improvement for the FOLFIRINOX arm in terms of the primary end point, overall survival (median of 11.1 *v* 6.8 months; $P < .001$; hazard ratio for death, 0.57). Additionally, more patients on the FOLFIRINOX arm were alive at specified landmark time points; patients on this arm demonstrated a 1-year survival rate of 48.4% compared with 20.6% on the gemcitabine arm. Other secondary end points, including median progression-free survival (6.4 *v* 3.3 months) and objective response rate (31.6% *v* 9.4%), were likewise significantly in favor of the FOLFIRINOX regimen.

A median survival of close to 1 year in a purely metastatic cohort has never before been approached in any phase III study of this disease. As such, the immediate question arises as to whether FOLFIRINOX should become the newly adopted standard of care for the front-line treatment of patients with metastatic pancreatic cancer, at least in those with preserved performance status. (Notably, patients enrolled onto this trial were required to have an Eastern Cooperative Oncology Group performance status of 0-1; there was also an upper-limit age cutoff at 76 years.) The authors offer an appropriately measured conclusion, noting in their final statement that FOLFIRINOX represents "a first-line option" (as opposed to the new gold standard) in this patient population. [3(p1824)] Why is it prudent for us to follow this lead, tempering our enthusiasm with an appropriate degree of caution?

First of all, not surprisingly, the FOLFIRINOX regimen was associated with higher rates of grade 3 and 4 toxicities than gemcitabine, including febrile neutropenia (5.4%), diarrhea (12.7%), and sensory neuropathy (9.0%). The incidence of severe toxicities is of paramount concern when weighing the risks and benefits of various therapies to determine which to offer patients in a noncurative setting. Additional measures that need to be accounted for but are not reported in this article[3] include the frequency of less severe (grade 1 or 2) toxicities and hospitalization rates. Other practical considerations, such as the minor inconvenience associated with infusional pump therapy and central catheters, also factor into medical decision making.

Importantly, despite the aforementioned toxicities, the time to definitive quality of life (QOL) degradation (as measured by a biweekly European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) was superior in patients who received FOLFIRINOX compared with gemcitabine, presumably because of a delay in disease progression that was associated with this treatment arm. Especially in pancreatic cancer, such QOL measures are an absolutely essential component of assessing the risk/benefit ratio of any new therapeutic option, given patients' short survival duration and the pain, anorexia, and inanition that so often accompanies the underlying disease process. (Recall, for instance, that clinical benefit response was used as the primary efficacy measure in the pivotal trial that led to the approval of gemcitabine for this disease.) Thus, inclusion of these QOL data are reassuring.

Perhaps even more so, one needs to ask whether the absolute magnitude of survival benefit that is conferred by FOLFIRINOX is clinically meaningful and worth the added risks and toxicities. The modest improvement in median survival of 0.33 months in the PA.3 trial (A Randomized Placebo Controlled Study of OSI-774 [TARCEVA] Plus Gemcitabine in Patients With Locally Advanced, Unresectable or Metastatic Pancreatic Cancer),[1] for example, helps explain why the combination of gemcitabine plus erlotinib has not gained more widespread traction for this disease indication. By comparison, an absolute incremental improvement in median survival of

greater than 4 months with FOLFIRINOX is quite striking. This result substantially exceeds those reported in pivotal trials that led to US Food and Drug Administration approval of other cytotoxic and targeted agents—not only erlotinib in advanced pancreatic cancer, but also bevacizumab in non–small-cell lung cancer[4] and irinotecan in metastatic colorectal cancer,[5] to cite a few examples. In a disease characterized by a median survival of less than 1 year, it is likely that few would argue that a survival benefit of this magnitude does not justify the added risk.

Next, as always, we need to ask whether the subjects enrolled onto this trial are representative of the average patient with pancreatic cancer. The majority of individuals (approximately 60%) who participated in this study had nonpancreatic head tumors, and as a result, only 14% had indwelling endobiliary stents. This distribution of pancreatic tumor location is the opposite of what one might typically expect to see in clinical practice; Surveillance, Epidemiology, and End Results data indicate a 3:1 ratio of pancreatic cancers located in the head versus the body or tail, when such data are captured.[6] Other multicenter trials of advanced pancreatic cancer similarly report the majority of tumors to arise within the pancreatic head.[7,8] Patients with obstructing pancreatic head lesions and indwelling biliary stents face infectious complications such as ascending cholangitis and biliary sepsis that could be potentially life threatening in the setting of profound myelosuppression. Thus, the FOLFIRINOX regimen, with its 46% rate of grade 3 to 4 neutropenia, could prove to be a prohibitively difficult regimen to administer in such patients, particularly in centers and locations where access to specialists for the endoscopic management of biliary complications may be limited. Certainly, the routine use of growth factor support as primary prophylaxis (which was not mandated in the French trial, but was eventually administered in 42.5% of patients on the FOLFIRINOX arm) is advisable in patients with preexisting endobiliary stents in whom this regimen is being considered.

On a related note, can we assume that the toxicity profile of FOLFIRINOX will be similar if administered to other, non-French populations? Previous analyses have demonstrated that the tolerability of fluoropyrimidines may differ by region, with East Asian patients experiencing the fewest and patients in the United States experiencing the most adverse effects.[9] Subgroup analysis of North Central Cancer Trials group 9741, a large colorectal cancer trial that evaluated several combination regimens that contained the same components as FOLFIRINOX, found significant differences in severe adverse event rates between white and black patients, likely reflecting marked racial differences in relevant pharmacogenetics.[10] Thus, the need to assess how well FOLFIRINOX is tolerated among different ethnicities and geographic regions would represent an important next step. This should not necessarily require duplicative phase III studies to be performed in the United States or other parts of the world, but it does mean that additional data for FOLFIRINOX must be accurately captured, reported, and disseminated so that we have a clearer sense of its portability and generalizability.

Although this trial was conducted exclusively in patients with metastatic pancreatic cancer, there will undoubtedly be tremendous interest in exploring FOLFIRINOX in patients with earlier stages of disease. In the setting of locally advanced unresectable pancreatic cancer, it would be appropriate to consider use of this regimen as part of induction chemotherapy, especially as one might expect a higher proportion of candidates to be fit enough to receive more aggressive chemotherapy. However, as many patients in this context receive multimodality therapy, we need greater experience to define the optimal duration that FOLFIRINOX can and should be given before consolidative chemoradiotherapy is administered. The relatively high objective response rates associated with this regimen also suggest its possible applicability as neoadjuvant therapy in patients with borderline resectable disease, for whom cytoreduction represents an important goal of therapy.

A number of other questions remain that may help us additionally refine our use of the FOLFIRINOX regimen. For example, are all of the individual components of FOLFIRINOX necessary, or can this combination somehow be simplified to improve tolerability without compromising efficacy? The combination of a fluoropyrimidine plus oxaliplatin has been examined in both the front-line and second-line settings for this disease indication.[11,12] In one large randomized phase II study that was conducted across multiple German centers, the doublet of capecitabine plus oxaliplatin produced a median overall survival of 8.1 months and median progression-free survival of 4.2 months in previously untreated patients with both metastatic and locally advanced disease, the majority (85%) of whom had a Karnofsky performance status of 80% or higher.[11] Recognizing the limits of cross-study comparisons, these efficacy results do not approach those observed with FOLFIRINOX, which suggests that the inclusion of irinotecan should be considered an essential part of this regimen, at least for now. There is also a common refrain that the bolus administration of fluorouracil may perhaps be a dispensable component of the modified de Gramont regimen, given that the 2-day infusion of this agent provides the essential means for drug delivery; however, this proposition has never been confirmed in a large randomized trial.

Looking ahead, the trial by Conroy et al[3] should serve as a springboard for contemplating and designing future studies in pancreatic cancer. These data suggest that we should be moving beyond gemcitabine as the reference standard in randomized clinical trial design. Even while we await additional validation of its safety and efficacy, it will be difficult—and perhaps ethically questionable—not to include FOLFIRINOX as a treatment arm in such studies. At the same time, recognizing that FOLFIRINOX will not be suitable for many patients, we now also have the opportunity to begin to develop parallel trials for patients with good versus poor performance status, with correspondingly different chemotherapy backbones for each.

Importantly, we do not know yet whether FOLFIRINOX will be a reasonable chemotherapeutic platform on which to build, or if the toxicities of this regimen will prove to be a significant barrier for the addition of novel targeted therapies. Our institution (University of California, San Francisco) has just recently opened a phase I trial of FOLFIRINOX plus an oral Hedgehog signaling inhibitor for advanced pancreatic cancer. Other studies in development are adopting a similar strategy, which should allow us to discover the doses of FOLFIRINOX that can safely be combined with these newer agents, or whether its dosing will be reduced to the extent that efficacy is potentially compromised. However, we should also not limit ourselves by thinking that FOLFIRINOX plus drug X represents the exclusive strategy in clinical trial design from this point forward, which is similar to what we have been doing for the past decade by adding drugs to gemcitabine. Preclinical studies of novel targeted agents may suggest greater synergy when combined with one chemotherapy platform versus another, and intratumoral biomarker analysis (always a challenge in metastatic

pancreatic cancer) may lend additional insight into the selection of the most appropriate chemotherapeutic regimen to use for any given patient. Such information should guide the design of clinical trials accordingly.

These are all key issues with which both national cooperative groups and pharmaceutical companies interested in pancreatic cancer drug development are currently wrestling. Such challenges notwithstanding, they represent a welcome and refreshing set of new considerations for us to ponder in a disease that has too often been met with frustration and nihilism in the past.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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