FOLFIRINOX in Locally Advanced Pancreas Adenocarcinoma: Back to the Future?

TANIOS BEKAI-SAAB AND RICHARD M. GOLDBERG

Section of Gastrointestinal Oncology, Division of Medical Oncology, Department of Medicine, The Ohio State University/Arthur James Cancer Hospital and Richard Solove Research Institute, Columbus, Ohio, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Tanios Bekai-Saab

Richard M. Goldberg

Both the incidence and mortality rate of pancreas adenocarcinoma are rising [1]. Following decades of slow progress in managing patients with advanced pancreas cancer, there are some indications that the treatment landscape, at least for advanced disease, is shifting in a meaningful way. In 2010, the ACCORD (Actions Concertées dans les Cancer Colo-Rectaux et Digestif) 11 study known as PRODIGE (Partenariat de Recherche en Oncologie Digestive) 4 suggested a significant benefit in terms of response, progression-free and overall survival in favor of FOLFIRINOX compared with the prior standard, single-agent gemcitabine [2]. This year, at the ASCO GI Symposium, we learned that patients treated with a regimen of albumin-bound paclitaxel and gemcitabine experienced a significant benefit in those three measures compared with those treated with gemcitabine alone [3].

Today, for patients with locally advanced pancreas adenocarcinoma, there is no internationally embraced standard treatment. Gemcitabine with or without radiation is considered to be an acceptable option [4]. The notable improvement in overall response rate for the combination regimens in advanced disease has led investigators to evaluate these regimens in the management of patients with locally advanced, unresectable disease. In particular, the favorable results with FOLFIRINOX led investigators to examine its utility in patients with borderline resectable and unresectable non-metastatic pancreas cancer, a setting in which a favorable treatment response could lead to resection for cure. A number of institutions are now reporting the results of their own experience with this regimen in this setting.

In this issue of *The Oncologist*, Faris et al. [5] report the results of the Massachusetts General Hospital experience with FOLFIRINOX chemotherapy followed by chemoradiation in patients with locally advanced unresectable pancreatic adenocarcinoma (LAPCA). Patients

initially received standard FOLFIRINOX as previously published. Neoadjuvant chemotherapy consisted of four cycles of FOLFIRINOX, followed by repeat imaging. Those patients who did not progress on therapy received four more cycles of FOLFIRINOX followed again by imaging. At that time, patients whose disease had not progressed received intensity-modulated radiation therapy (50.4 Gy) along with infusional 5-fluorouracil or capecitabine as a radiosensitizer. In 22 patients with LAPCA, they found a response rate of 27.3% with 5/22 patients undergoing R0 resections (R0 resection indicates a microscopically ≥ 1 mm margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed) following treatment. Unfortunately, three of those resected patients had recurrences in the first 5 months following surgery. The authors of this study also noted significant toxicities, including at least one emergency room visit or hospitalization for 32% of the patients.

What other data do we have regarding this approach from other reports? A recently published study by Hosein et al. found similar results in fourteen unresectable patients [6]. However, unlike the experience in the Faris study, patients in this cohort did not receive additional neoadjuvant chemoradiation unless their disease remained unresectable after initial chemotherapy. The addition of chemoradiation helped convert initially unresectable disease to resectable disease in three patients, resulting in a 43% R0 resection rate. Results of another retrospective study by Boone et al. [7] were presented at the 2013 ASCO GI Symposium. Patients from this LAPCA cohort ($n = 10$) received standard FOLFIRINOX, and two subjects achieved an R0 resection. Overall, about one third of patients received chemoradiation as part of their neoadjuvant regimen, although the authors did not delineate the criteria used to integrate this intervention. Similar to the experi-

Correspondence: Tanios Bekai-Saab, MD, The Ohio State University – James Cancer Hospital, A454 Starling Loving Hall, 320 West 10th Avenue, Columbus, OH 43210. Telephone: 614-293-9863; Fax: 614-293-4372. E-Mail: Tanios.Bekai-Saab@osumc.edu. Received April 30, 2013; accepted for publication May 2, 2013. ©AlphaMed Press 1083-7159/2013/\$20.00/http://doi.org/10.1634/theoncologist.2013-0157.

ence in other studies, the regimen was found to be relatively toxic with a large proportion—16%—of subjects dropping out of the trial during treatment. Mahaseth et al. also reported an experience with a modified form of FOLFIRINOX (omitting the bolus 5FU and adding pegfilgrastim support) in an LAPCA cohort of 20 patients, 15% of whom underwent an R0 resection rate, with less than expected toxicities [8]. There are five other small retrospective studies reporting results in LAPCA with FOLFIRINOX with or without chemoradiation suggesting similar response rates, although in these series, R0 resection rates were not reported [9-13].

What do the collective results of all these small retrospective studies tell us with regard to the treatment of locally advanced pancreas adenocarcinoma? It is certainly encouraging to see relatively consistent results across all studies, but the retrospective nature of these series and their small sample sizes leaves us with uncertainty regarding the utility of this approach. There are a number of questions that remain to be answered before any meaningful conclusion can be drawn. Does the ability to perform an R0 resection improve the chance of a cure? We know from series conducted in patients with clearly resectable pancreatic adenocarcinoma that the overwhelming majority of patients with R0 resection (even in the presence of negative lymph nodes) still die from metastatic disease [14]. This could be explained by the aggressive nature of pancreas adenocarcinoma, a tumor that commonly exhibits early micrometastatic disease and dissemination prior to diagnosis; preoperative treatment with one or more modalities, followed by surgical extirpation of visible or measurable disease nearly always leaves behind micrometastatic disease [15]. Improved systemic control facilitated by intensive combination chemotherapy, if achievable, might translate to improved chances of long-term remission and cure.

With this in mind, what does additional local therapy such as radiation contribute to the disease-control strategy? In the present MGH study, all patients whose disease had not progressed during initial FOLFIRINOX were treated with preoperative chemoradiation, whereas in the study from Hosein this combined modality was delivered only in those patients whose tumors did not become resectable following chemotherapy. Most studies in LAPCA suggest that radiation therapy is best sequenced following 3-4 months of chemotherapy in those patients who do not manifest systemic recurrence during that interval [16]. However, the validity of this conclusion is uncertain because of the lack of adequate prospective randomized trials that control for selection bias and other variables. In future studies, a strong case can be made to improve selection of patients who are most likely to benefit from neoadjuvant chemoradiation by limiting its use to those who remain unresectable (or have borderline resectability) following FOLFIRINOX. In view of the continued controversy regarding the role of radiation in pancreas adenocarcinoma, it is essential that future studies in this setting address whether this additional modality provides an incremental benefit given its potential cost and toxicity.

A number of other challenges remain in the effort to optimize the usage of FOLFIRINOX in the setting of LAPCA. The limited course of therapy using this aggressive regimen in the neoadjuvant setting is an attractive approach, as compared to its open-ended use in the palliative management

of metastatic disease. However, the above studies suggest that the risk of introducing significant toxicity is an important consideration in a patient population that typically has a better performance status and thus weathers the rigors of this regimen better than sicker patients with metastatic disease. This emphasizes the importance of studying FOLFIRINOX prospectively in the United States, as previous analyses in other malignancies suggest regional and ethnic differences in the toxicity profile of fluoropyrimidines [17]. A closer dissection of the various studies that were published or presented suggests various strategies for “fine tuning” the dose intensity of FOLFIRINOX. These strategies might include starting initially with FOLFOX and then adding irinotecan according to individualized assessment of the regimen’s tolerability. Additional approaches to increasing tolerability would include applying calculated dose reductions compared to the original regimen and employing growth factor support at treatment initiation [9-13]. Future studies could consider decreasing the bolus dose of 5-fluorouracil and leucovorin and perhaps applying initial dose reductions to irinotecan. Many institutions, including ours, have already adopted such modifications. If the application of this aggressive strategy does not translate into additional cures, is it worth the cost of toxicity? Faris et al. showed that in the first 5 months, three out of the five patients who had undergone resections showed evidence of recurrence. On the other hand, Hosein et al. reported that only one of their seven resected patients manifested recurrent disease after a median follow up of 13.4 months. These variable results again demonstrate the importance of well-controlled, prospectively designed studies. Overall, however, if these results hold true going forward, the challenge is to improve further the “curability factor.”

We appear to be reaching a plateau in the results achieved when deploying cytotoxic therapies (including radiotherapy) in LAPCA. The last few years have witnessed significant progress in our knowledge of the molecular and genetic basis of pancreas adenocarcinoma, helping to create a better understanding of valid molecular therapeutic targets [18,19]. FOLFIRINOX, because of its intensity, presents a challenging platform on which to build rational combinations with targeted agents. Tumor response rates have proven to be a useful surrogate for predicting the value of chemotherapy in improving resectability and prolonged survival in borderline resectable and unresectable patients with liver metastasis in colorectal cancer [20]. Gemcitabine combined to albumin-bound paclitaxel nearly tripled the likelihood of response versus gemcitabine alone and may represent a more practical chemotherapeutic platform to build upon. Unfortunately, there is limited experience with this combination in the earlier stages of this cancer, and we do not have any direct comparative data for the efficacy of gemcitabine and albumin-bound paclitaxel versus FOLFIRINOX.

For many decades, advances in the management of pancreas adenocarcinoma have been handicapped because of the difficulties in developing new agents, the retrospective nature of many studies, and the shaky evidence for efficacy based upon underpowered trials. The data presented in the studies mentioned in this editorial, including the one by Faris et al., suggest that this may be a promising strategy in LAPCA, but such small retrospective reports do not establish a stan-

dard of care given the multitude of unanswered questions that remain. Looking “back to the future,” the vehicle to answer those questions is the well-designed prospective and adequately powered randomized trial, and thankfully a number of such studies are already underway. Recent history taught us that the introduction of FOLFIRINOX in advanced disease management was met with some resistance due to an unwavering allegiance to the modestly effective use of gemcitabine in pancreas cancer. To continue improving the survival rate in pancreas adenocarcinoma, we need both to understand the molecular genetics of the disease and to think innovatively about new approaches. It seems clear that our current armamentarium of cytotoxic agents with or without radiation

will not defeat this disease, although the approach reported by the MGH group in this issue may help some patients get to resection, a few of whom may have the potential for long-term, disease-free survival. This retrospective analysis, while limited for obvious reasons, enriches our understanding of the benefits and pitfalls of aggressive therapy.

DISCLOSURES

Tanios Bakaii-Saab: Amgen, BMS, Bayer/Onyx, Genentech, Sanofi (C/A); Onyx, Pfizer (RF); **Richard Goldberg:** Amgen, Bayer, Genentech, Genomic Health, Lilly, & Sanofi Aventis (C/A); Amgen, Bayer, Genentech, Myriad, Sanofi Aventis, Enzon (RF).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
2. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
3. Von Hoff DD, Ervin TJ, Arena FP et al. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT) *J Clin Oncol* 2012;30:(LBA148).
4. Huguet F, Girard N, Guerche CS et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. *J Clin Oncol* 2009;27:2269–77.
5. Faris JE, Blaszkowsky LS, McDermott S et al. FOLFIRINOX in Locally Advanced Pancreatic Cancer: The Massachusetts General Hospital Cancer Center Experience. *The Oncologist* 2013;18:543–548.
6. Hosein PJ, Macintyre J, Kawamura C et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 2012;12:199.
7. Boone B, Stevie J, Krasinskas A et al. Outcomes with FOLFIRINOX for locally advanced pancreatic cancer. *J Clin Oncol* 2012;30 (suppl 34; abstr 256).
8. Mahaseth H, Kauh JS, Brucher E et al. Safety and efficacy of modified FOLFIRINOX in pancreatic cancer: A retrospective experience. *J Clin Oncol* 2012;30 (suppl; Abstr e14614).
9. Peddi PF, Lubner S, McWilliams R et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. *JOP* 2012;13:497–501.
10. Gunturu KS, Thumar JR, Hochster HS et al. Single institution experience with FOLFIRINOX in advanced pancreatic adenocarcinoma (PC). *J Clin Oncol* 2012;30 (suppl 4; abstr 330).
11. Lowery MA, Yu KH, Adel NG et al. Activity of frontline FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at MSKCC. *J Clin Oncol* 2012;30:abstr 4057.
12. Vasile E, De Lio N, Cappelli C et al. Neoadjuvant modified FOLFOXIRI in locally advanced pancreatic cancer [abstract 714P]. *Ann Oncol* 2012;23(suppl 9):ix238.
13. Mathey L, Sa-Cunha A, Blanc JF et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicentric prospective study [abstract 716P]. *Ann Oncol* 2012;22(suppl 9):ix238.
14. Chang DK, Johns AL, Merrett ND et al. Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol*. 2009;27:2855–62.
15. Kayahara M, Funaki K, Tajima H et al. Surgical implication of micrometastasis for pancreatic cancer. *Pancreas*. 2010;39:884–8.
16. Huguet F, André T, Hammel P et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol*. 2007;25:326–31.
17. Haller DG, Cassidy J, Clarke SJ et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol*. 2008;26:2118–23.
18. Jones S, Zhang X, Parsons DW et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008;321:1801–1806.
19. Tuveson DA, Neoptolemos JP. Understanding metastasis in pancreatic cancer: A call for new clinical approaches. *Cell* 148:21–23.
20. Alberts SR. Update on the optimal management of patients with colorectal liver metastases. *Crit Rev Oncol Hematol*. 2012;84:59–70.

EDITOR’S NOTE: Please see the accompanying article on pages 543–548 of this issue.