FOLFIRINOX: Desert, Oasis, or Mirage?

Cristina R. Ferrone, MD

Massachusetts General Hospital, Surgery, Boston, MA

Unfortunately, most patients with PDAC present with advanced disease. In addition to the large number who present with distant metastases, approximately 40 % of patients with pancreatic adenocarcinoma present with locally advanced or borderline resectable disease (LAPDC).¹ Furthermore, systemic disease is identified in 30 % of patients with LAPDAC during early cycles of treatment.² The cynics believe that a much larger percentage, if not all, of these patients have micrometastatic disease at the time of diagnosis. The understanding that locally advanced and borderline resectable lesions are more advanced and that an R1 resection decreases overall survival has prompted aggressive neoadjuvant approaches.^{3,4} Based on the ACCORD-11 trial different institutions have utilized FOLFIRINOX in patients with locally advanced and borderline resectable PDAC.^{5–8} Similar to Blazer et al.'s results, this has resulted in increased resectability rates. Until recently, only 30 % of patients were converted from unresectable to resectable candidates with chemotherapy and/or chemoradiation therapy.⁹ In the series by Blazer et al., 51 % of patients became resectable after 4 months of modified FOLFIRINOX $\pm$ chemoradiation, and progression was seen in only 15 % of patients.

While some of the responses to FOLFIRINOX followed by chemoradiation have been dramatic, there is a price to pay. Patients receiving FOLFIRINOX often experience neutropenia (22 %), febrile neutropenia (17 %), thrombocytopenia (11 %), diarrhea (11 %), and neuropathy, resulting in hospital admissions for 32 % of patients.^{10,11} FOLFIRINOX is clearly a difficult regimen which will affect the quality of life of even the strongest patients. To decrease the morbidity of treatment Blazer et al. modified

the regimen by decreasing the irinotecan dose and getting rid of the bolus 5-FU and leucovorin. With these modifications, none of the patients were admitted with febrile neutropenia, and only three were admitted for diarrhea/dehydration.

Most cancer patients and caregivers agree that goals of care include quality and quantity of life. What price are we willing to pay for the hope of an improved long-term survival? For each patient, this equation is different. While FOLFIRINOX has clearly improved overall survival in patients with metastatic pancreatic adenocarcinoma, its role in locally advanced and borderline cancers is unclear.

From the time of diagnosis to recovery from the operation, the patient will have withstood 8 months of therapy, in the best case scenario. Often the 4 months of FOLFIRINOX are followed by 3–6 weeks of chemoradiation. We then hope to resect the cancer. So, is 8 months of therapy that significantly affects quality of life worth it? We don't know, but we hope so! We are hopeful that the tenets of the past still hold true and that resection improves survival. In our experience with neoadjuvant FOLFIRINOX, 92 % of patients had an R0 resection and 65 % had node-negative disease.^{5,8} In the series by Blazer et al., patients who underwent resection had a statistically significant improvement in survival compared with patients who were not resected. In our series, patients treated with FOLFIRINOX had an improved overall survival compared with patients who had clearly resectable cancers and received no neoadjuvant therapy. Currently, all of the data looking at FOLFIRINOX in patients with LAPDAC and borderline cancers are small retrospective series. Are we sure that we are improving overall survival or have we just selected patients with a better performance status and better biology?

We know for some patients a complete pathologic response is achieved, whereas others will recur within 6 months of their operation. Identifying predictors of early recurrence and nonresponders will be essential as we move forward with this and other aggressive treatment strategies.

What if FOLFIRINOX really is turning the desert into an oasis? If the results published by Blazer et al. and those that our group and others have documented are validated by a clinical trial, should any patients with PDAC go to the operating room without neoadjuvant therapy? There are few tumors that would benefit as much as PDAC from effective neoadjuvant therapy. Even at high-volume centers, the morbidity of pancreatic resection is approximately 40 and 25 % of patients never receive adjuvant therapy.^{12,13} If the increase in the R0 resection rate and decrease in lymph node positivity translates into improved survival, neoadjuvant therapy should be strongly considered in every patient. Modifications in FOLFIRINOX dosing and administration without losing efficacy, as has been done by Blazer et al., will be essential to minimizing the toxicity and improving quality of life during treatment and extending overall survival. Time and experience will reveal the truth: oasis versus mirage.

REFERENCES

1. Zakharova OP, Karmazanovsky GG, Egorov VI. Pancreatic adenocarcinoma: outstanding problems. *World J Gastrointest Surg.* 2012;4(5):104–13.
2. He J, et al. Management of borderline and locally advanced pancreatic cancer: where do we stand? *World J Gastroenterol.* 2014;20(9):2255–66.
3. Konstantinidis IT, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a “true” R0 resection? *Ann Surg.* 2013;257(4):731–6.
4. Evans DB, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3496–502.
5. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg.* 2015.
6. Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364(19):1817–25.
7. Christians KK, et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist.* 2014;19(3):266–74.
8. Ferrone CR. Lymphadenectomy for pancreatic neuroendocrine tumors: is that the relevant debate? *Ann Surg.* 2014;259(2):213–4.
9. Gillen S, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med.* 2010;7(4):e1000267.
10. Faris JE, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist.* 2013;18(5):543–8.
11. Hosein PJ, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer.* 2012;12:199.
12. Fong ZV, et al. Understanding hospital readmissions after pancreaticoduodenectomy: can we prevent them? A 10-year contemporary experience with 1,173 patients at the Massachusetts General Hospital. *J Gastrointest Surg.* 2014;18(1):137–44; discussion 144–5.
13. Ahmad SA, et al. Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1,302 patients. *Ann Surg.* 2012;256(3):529–37.