

## EDITORIAL

## Predicting a Response to FOLFIRINOX in Pancreatic Cancer

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Cancer of the pancreas is highly lethal and it is the fourth leading cause of cancer death in the United States (1). The majority of patients with pancreatic cancer have metastatic disease at the time of diagnosis, and the few patients who present with localized disease often develop metastases within two years of their surgery. Recently, the combination regimens of FOLFIRINOX (2) and Gemcitabine/Nab-paclitaxel (3) have provided hope for patients with metastatic disease and also for patients with locally advanced and potentially resectable disease. In the metastatic setting, median survival has been pushed out to beyond 11 and eight months, respectively, and we are now seeing approximately 10% of patients alive at two years (2–4). Several institutions have now published data about their ability to convert locally advanced or borderline resectable disease to resectable by using FOLFIRINOX (5–7).

Clearly, FOLFIRINOX represents an advance in the treatment of patients with pancreatic cancer, but it is an aggressive regimen with considerable side effects. Often, oncologists limit this regimen to carefully selected patients with good performance status and minimal comorbidities. Even then, dose modifications, treatment alterations, and the use of growth factors are frequently required to help make this regimen more tolerable for patients. Identifying which patients will most likely benefit from FOLFIRINOX with a predictive marker would help guide treatment strategies and improve outcomes. Specifically, knowing which patients are more likely to respond to FOLFIRINOX would help patients and providers make more informed decisions. Recently, Waddell and colleagues reported a small experience of pancreatic cancer patients with defective DNA maintenance (8). They found that defects in DNA maintenance may predict chemosensitivity to platinum-based therapy and thus hypothesized the potential for this as a biomarker needing further investigation.

In this issue of the Journal, Cappo et al. chose a different tack by attempting to exploit the pharmacology of irinotecan in order to establish a predictive biomarker (9). Irinotecan was the first camptothecin to enter clinical trials in the 1980s, and it is the most widely used camptothecin in the clinic today. Irinotecan gets converted by carboxylesterase converting enzyme to SN-38,

the active metabolite. Subsequently, SN-38 is glucuronidated in the liver and then excreted in the bile. The main carboxylesterase responsible for the activation of irinotecan is thought to be located in the liver; however, irinotecan is a relatively poor substrate for human liver carboxylesterase. Carboxylesterase activity has been noted in human tissues, including various cancers, but it remains unclear how much this influences both the pharmacokinetics and the pharmacodynamics of irinotecan (10). A study of carboxylesterase in human colon tumors demonstrated a more than 100-fold variation in the levels of carboxylesterase (11). Although irinotecan has been standard first- or second-line therapy in colon cancer for over 15 years, we still do not reliably know whether carboxylesterase activity corresponds with response to therapy. Compared with the wealth of pharmacodynamic studies evaluating variation in glucuronidation and its effect on irinotecan toxicity, there is a relative dearth of studies evaluating carboxylesterase and response to therapy.

Capello and colleagues in the accompanying article investigated the value of carboxylesterase 2 (CES2) as a potential predictive marker for patients receiving neoadjuvant FOLFIRINOX. They hypothesized that high expression of CES2 would enhance efficacy of the FOLFIRINOX regimen. The authors found that CES2 was elevated in pancreatic cancer cell lines more so than other cell lines, but also with heterogeneity in expression levels. Over 60% of pancreatic cancer tissue samples taken from patients who did not receive neoadjuvant therapy expressed CES2, and over 40% of these patients demonstrated high CES2 expression. They found higher CES2 expression in pancreatic cancer tissue compared with normal pancreatic tissue. Although they did not show this data, the authors found that CES2 was not prognostic, as survival did not differ between patients based on their CES2 expression. Importantly, the authors demonstrated an inverse relationship between CES2 activity and the half maximal inhibitory concentration (IC50) of irinotecan. Thus, as CES2 activity increased, the amount of irinotecan needed for a response decreased. The investigators then evaluated 22 patients with resected pancreatic cancer who had received neoadjuvant FOLFIRINOX prior to their cancer surgery. Higher levels of CES2 were associated with longer overall survival and progression-free

survival. Tumor size and CES2 expression were the only predictors of overall survival.

We commend Capello et al. for their work. In an era where DNA signatures rule the day, the authors relied on basic pharmacology to find a potentially important biomarker. While precluding definitive conclusions because of the small sample size, the clinical findings were consistent with their laboratory results. The authors decided to concentrate on overall survival in patients undergoing preoperative therapy, presumably because of the availability of tissue and the uniformity of treatment, but this can be a very heterogeneous group of patients. Although it would have been reassuring to know that response rate correlates with CES2 expression, assessing response rates in patients with localized or borderline resectable cancers is fraught with difficulty because of inflammation around the tumor. Furthermore, recent work has demonstrated that radiographic response after preoperative FOLFIRINOX is unreliable (12). Nevertheless, the findings from this manuscript open a world of possible investigations. It remains unclear whether CES2 expression fluctuates within an individual's tumor and whether treatment with chemotherapy or radiation changes expression. We also do not know whether CES2 expression differs in primary vs metastatic sites. The results of this work should encourage investigators to study how CES2 expression correlates with response to FOLFIRINOX in the metastatic setting, where it is most widely used. Additionally, these findings should be combined with the recent findings regarding platinum sensitivity in pancreatic cancer (8). Lastly, beyond pancreatic cancer, we need to determine the applicability of this approach in colon cancer and gastric cancer, where irinotecan is a standard therapy.

It is amazing that after nearly 15 years of use in the clinic, we still have much to learn about irinotecan. Furthermore, it is a welcome reminder that we need to understand the pharmacology of our drugs and how pharmacodynamic effects are influenced by both the normal and tumoral expression of

metabolizing and activating enzymes. We look forward to the research and investigations that the findings from this manuscript will help motivate.

## Notes

The authors have no conflicts of interest to disclose.

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