Clinics in Surgery

Case Report
Published: 05 Dec, 2016

Sinusoidal Obstruction Syndrome after Neoadjuvant FOLFIRINOX for Locally Advanced Pancreatic Cancer

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Abstract

Case Report: A 69-year-old woman diagnosed with locally advanced pancreatic adenocarcinoma due to significant vascular involvement underwent 11 cycles of FOLFIRINOX neoadjuvant chemotherapy. After satisfactory imaging response, the tumor was resected with a pancreaticoduodenectomy procedure with superior mesenteric and portal vein reconstruction. At surgical exploration, the patient's liver had the appearance of a "blue liver," consistent with sinusoidal congestion or obstruction, but otherwise the liver was normal size without any metastasis. A day after her surgery, the patient became acidotic, anuric, and pressor dependent, succumbing to multisystem organ failure that evening. FOLFIRINOX contains oxaliplatin, a drug strongly correlated with an increased risk of sinusoidal obstruction syndrome. As neoadjuvent chemotherapy containing oxaliplatin becomes more widely used for locally advanced pancreatic cancer, more research is needed to understand the implications of oxaliplatin toxicity and pancreatic resections to reduce potential perioperative complications with particular attention to patients receiving higher cycle counts of FOLFIRINOX or other oxaliplatin-based treatments.

Introduction

Neoadjuvant chemotherapy is increasingly used for locally advanced pancreatic adenocarcinoma as an effective treatment strategy to qualify patients for potentially curative surgery. Although current neoadjuvant regimens might include traditional gemcitabine-based chemotherapies, newer oxaliplatin combination chemotherapy regimens have been enthusiastically adopted since 2011, following the landmark trial[1] that demonstrated the efficacy of FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) for metastatic pancreatic cancer. Here we present a case of a patient who received neoadjuvant FOLFIRINOX for locally advanced pancreatic cancer. After eleven cycles of FOLFIRINOX, she became eligible for a pancreaticoduodenectomy. Unfortunately, the day after her surgery she succumbed to liver failure. In this case study we suggest that her complication was possibly related to her FOLFIRINOX chemotherapy regimen.

Case Presentation

A 68-year-old woman with a history of hypertension and coronary artery disease presented with decreased appetite, rapid weight loss (13lbs in 4 weeks), increasing fatigue, and upper abdominal symptoms (burning, nausea, and epigastric pain). CT imaging identified a mass encasing the celiac axis with significant involvement with the superior mesenteric and portal vein (Figure 1). FNA confirmed a diagnosis of pancreatic adenocarcinoma in the head of the pancreas that also extended into the neck region. Initial clinical staging based on imaging was T4NxM0. With this diagnosis, the patient started neoadjuvant chemotherapy with a plan for evaluation every three months to assess resectability. In December 2014 she started a first line regimen of gemcitabine and paclitaxel, completing a total of four cycles. During this first line treatment, in February 2015, she experienced symptoms of early satiety and intolerance of oral solids in the absence of mechanical obstruction and was started on parenteral nutrition.

Despite completing a full treatment regimen of gemcitabine and paclitaxel in early April 2015 there was persistent soft tissue around the celiac axis, attenuation of the proximal portal vein, and increased soft tissue anterior to the inferior vena cava, extending to the right pararenal fascia. In late April 2015, the patient started a second line of therapy with FOLFIRINOX with a total of eleven rounds (111 mg/m^2 of oxaliplatin, 522 mg/m^2 of leucovorin, 235 mg/m^2 of irinotecan, and a total of 3652 mg/m^2 of fluorouracil). She tolerated the first nine rounds of FOLFIRONOX

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Received Date: *20 Sep 2016*
Accepted Date: *22 Nov 2016*
Published Date: *05 Dec 2016*

Citation:
Schrope BA. Sinusoidal Obstruction Syndrome after Neoadjuvant FOLFIRINOX for Locally Advanced Pancreatic Cancer. Clin Surg. 2016; 1: 1250.

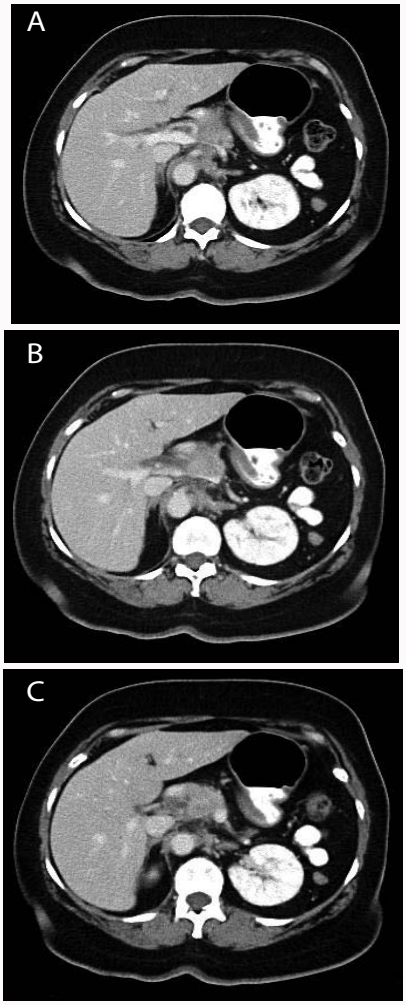

Figure 1: Pre-FOLIFIRINOX (11-15-2014) CT images showing the narrowing of the portal vein, encasement of the celiac axis and involvement of the SMV.

well, but by October 2015, after her ninth round, she developed thrombocytopenia, requiring suspension of FOLFIRINOX for two weeks. Once her platelet count rose, she resumed with her tenth round of FOLFIRINOX followed by another two week break and then a final eleventh round of FOLFIRINOX. She maintained consistent body weight throughout the FOLFIRINOX regimen, although she did have nightly TPN, eating two small meals a day.

After eleven cycles of FOLFIRINOX, the mass had decreased to 2cm (Figure 2), and it was determined in December 2015 she was a candidate for resection: a pancreaticoduodenectomy procedure with superior mesenteric and portal vein reconstruction. Upon exploration, her liver had the appearance of a "blue liver," consistent with sinusoidal congestion or obstruction but otherwise the liver was normal size without any metastasis.

During the operation there was minor but persistent bleeding throughout the case suggestive of mild portal hypertension, but at the time it was believed the bleeding was related to the superior mesenteric vein involvement and would be relieved by the reconstruction. The total clamp time was 83 minutes, but portal flow was maintained through the inferior mesenteric and splenic veins save for 18 minutes of total exclusion. Upon completing the pancreaticoduodenectomy and venous reconstruction with an inner jugular graft, there was no palpable pressure gradient across the graft. She was transferred to the surgical intensive care unit, intubated off pressors.

Starting the morning after surgery, she had a rapid rise in her AST and ALT levels to the 3000s and 2000s respectively. Doppler ultrasound was performed that showed patent left portal and hepatic veins but low blood flow to both the hepatic artery and right posterior portal vein. The patient became acidotic, anuric, and pressor dependent. She was brought emergently to the operating room for evaluation. Upon exploration, the vascular anastomosis was soft and intact, and flow was confirmed by Doppler ultrasound. The hepatic artery also demonstrated a palpable pulse, which was confirmed by ultrasound. The liver looked and felt congested. She was made comfort care by her family and succumbed to multisystem organ failure that evening.

Literature Review

There are limited chemotherapy options for locally advanced pancreatic cancer. The oldest regimen to treat pancreatic cancer is fluorouracil. In1997 gemcitabine was introduced as an alternative to fluorouracil after a randomized controlled trial with both metastatic and locally advanced pancreatic cancer patients demonstrated that a first line therapy with gemcitabine resulted in an improved survival of 1.2 months over fluorouracil [2]. Further advances in chemotherapy treatment occurred in 2011 when the PRODIGE 4/ACCORD 11 randomized trials demonstrated that the median overall survival for patients treated with FOLFIRINOX was 4.3 months longer than those treated with gemcitabine [1]. Since then, FOLFIRINOX has become a preferred chemotherapy treatment. A recent 2015 patient-level meta-analysis of 13 FOLFIRINOX studies suggested an even longer median overall survival of 24.2 months for FOLFIRINOX [3].

Today, FOLFIRINOX is frequently used in the neoadjuvant setting to downsize borderline resectable patients because it improves the overall survival rate and slows progression of the cancer [4]. The standard recommended regimen for FOLFIRINOX includes 85 mg/m^2 of oxaliplatin, 400 mg/m^2 of leucovorin, 180 mg/m^2 of irinotecan, and a total of 2800 mg/m^2 of fluorouracil, all of which is administered intravenously once every two weeks. Of course, each patient is different and can tolerate varying levels of the individual drugs as well as different number of cycles of the regimen.

The combination of chemotherapy drugs in FOLFIRINOX, however, is not new to the oncology landscape. The combination is very similar to colorectal cancer regimens that have been used for years. Although FOLFIRINOX for pancreatic cancer in the literature is reported to be "safe" with increased resection rates and better overall survival [3-6], there is a sizable body of literature since 2004 from colorectal cancer researchers, documenting the strong correlation between oxaliplatin and sinusoidal obstruction syndrome [7-11]. In 2004, Rubbia-Brandt et al. [7] found that 78% (34 of 43) of patients treated with oxaliplatin-based neoadjuvent chemotherapy developed sinusoidal dilation. Furthermore, oxaliplatin was also associated with other hepatic injuries including hepatocyte atrophy, perisinusoidal fibrosis, and nodular regenerative hyperplasia [7]. Subsequent studies after 2004 found anywhere from 10% to 61% of patients treated with oxaliplatin also had sinusoidal dilatation [12-14]. Many of these studies also found that there is some evidence that oxaliplatin increased morbidity although not mortality [8,14,15]. In two of these studies liver failure was a complication of surgical patients who developed sinusoidal obstruction syndrome (SOS) presumably from the oxaliplatin-based chemotherapy [15,16].

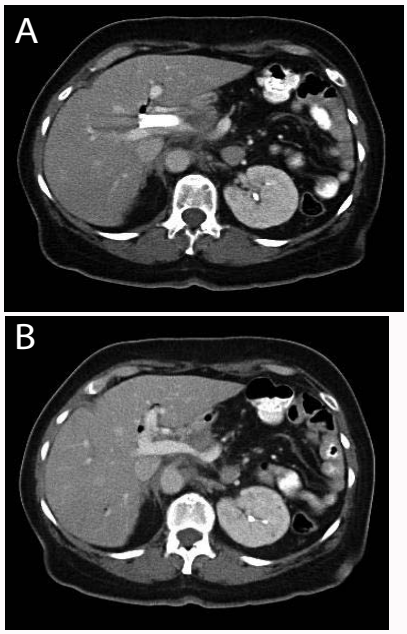

Figure 2: Post-FOLIFIRINOX (11-20-2015) CT images showing (a) a decreased narrowing of the portal vein and (b) a clear fat plane with the tumor regressing from the SMV.

Although the pathogenesis of oxaliplatin related sinusoidal obstructive syndrome is not fully understood, studies suggest it is directed against the endothelial cells of the hepatic sinusoids, enlarging the space of Disse [8,17-19]. It appears that oxaliplatin also affects the platelets in the liver and that thrombocytopenia occurs at an earlier stage for patients treated with oxaliplatin [18]. Unfortunately, there is no clear biomarker for these changes in the hepatocytes, so the gold standard for diagnosing SOS is still histopathology [19-23].

Additionally, FOLFIRINOX contains irinotecan, which is also associated with liver toxicity. Several studies correlate irinotecan with steatohepatitis [24], suggesting that higher dosages of FOLFIRINOX can increase the risk of hepatic toxicity.

Marsh et al. [25] 2015 review of FOLFIRINOX highlights several important unanswered questions about the use of FOLFIRINOX for pancreatic cancer patients including the best management practices and number of cycles, noting that the "optimal number of treatment cycles is not well understood." Marsh is also the first to remind the pancreatic cancer community that sinusoidal obstruction syndrome is associated with oxaliplatin. The dangerous unknown is the appropriate dosing of FOLFIRINOX. A 2016 patient-level meta-analysis of thirteen FOLFIRINOX studies only had a mean cycle count of six cycles [3]. This meta-analysis demonstrates many benefits of FOLFIRINOX, yet the safety of FOLFIRINOX at higher doses is still unknown. No articles have been published analyzing the consequences of higher cycle counts of FOLFIRINOX, specifically patients receiving higher doses of oxaliplatin.

Discussion

This case study highlights a potential caution when planning complex pancreatic surgery that includes vascular reconstruction in patients who have received an oxaliplatin-based regimen. Patients who receive a higher number of cycles of oxaliplatin may be vulnerable to the development of SOS. It is well recognized in the literature that liver resection under these circumstances can result in liver injury or failure because the liver is unable to appropriately regenerate, or the body is unable to respond to rapid exacerbation in portal hypertension from loss of parenchyma. Although the liver was not resected in the current case, the clamp time required to reconstruct the mesenteric system appears to have overwhelmed this fragile liver. Resection where the hepatoduodenal ligament is clamped and blood flow to hepatocytes is reduced in patients with SOS may exacerbate both ischemic and reperfusion injuries, risking the development of liver failure.

Although our experience is only a single case, the pancreatic surgery community must be made aware of this potential issue. New, similar cases should be reported so that an analysis of both preoperative (dosing, number of cycles, time between last dose and surgery) and operative (clamp time) factors can be conducted. This analysis is requisite to guide decisions about neoadjuvant therapy, timing of surgery, and resectability.

Conclusion

Oxaliplatin has been correlated with increased risk of sinusoidal obstruction syndrome for colorectal cancer patients. As neoadjuvent chemotherapy becomes the standard for locally advanced pancreatic cancer patients, more research is needed to understand the correlation between oxaliplatin and pancreatic cancer patients to reduce potential perioperative complications with particular attention paid to patients receiving higher cycle counts of FOLFIRINOX or other oxaliplatin-based treatments.

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