Clinics in Surgery

Case Report
Published: 05 Dec, 2016

Sinusoidal Obstruction Syndrome after Neoadjuvant Folfirinox for Locally Advanced Pancreatic Cancer

*Garrick Trapp, Michael D. Kluger, Stephen M. Schreibman and Beth A. Schrope**

Department of Surgery, Pancreas Center, Columbia University Medical Center, USA

Abstract

A 69-year-old woman diagnosed with pancreatic adenocarcinoma underwent 11 cycles of FOLFIRINOX. Despite some minor complications, she mostly tolerated the neoadjuvant chemotherapy therapy. After eleven cycles of FOLFIRINOX, the mass had decreased, and it was determined she was a candidate for resection: a pancreaticoduodenectomy procedure with superior mesenteric and portal vein reconstruction. Upon the exploratory laparoscopy, she 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 and succumbed to multisystem organ failure that evening. FOLFIRINOX contains oxaliplatin and there is a strong, documented correlation between oxaliplatin and an increased risk of sinusoidal obstruction syndrome in colorectal cancer patients. As neoadjuvant 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.

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 (13 lbs in 4 weeks), increasing fatigue, and upper abdominal symptoms (burning, nausea, and epigastric pain). CT imaging identified a mass encasing the celiac axis and adjacent to the common bile duct and splenic artery. The pancreatic duct distal to the mass was dilated to 4mm (Figure 1). A 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 T4N x M0. With this diagnosis, the patient started neoadjuvant chemotherapy with a plan for evaluation every three months to determine a change in 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, which extended 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 well. Yet by October 2015, after her ninth round, she developed thrombocytopenia, requiring suspension

OPEN ACCESS

Correspondence:
Beth A. Schrope, Department of Surgery, Pancreas Center, Columbia University Medical Center, 161 Fort Washington Ave, 9th Floor, New York, NY 10032, USA,
E-mail: bs170@cumc.columbia.edu

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

Citation:
Trapp G, Kluger MD, Schreibman SM, Schrope BA. Sinusoidal Obstruction Syndrome after Neoadjuvant Folfirinox for Locally Advanced Pancreatic Cancer. Clin Surg. 2016; 1: 1199.

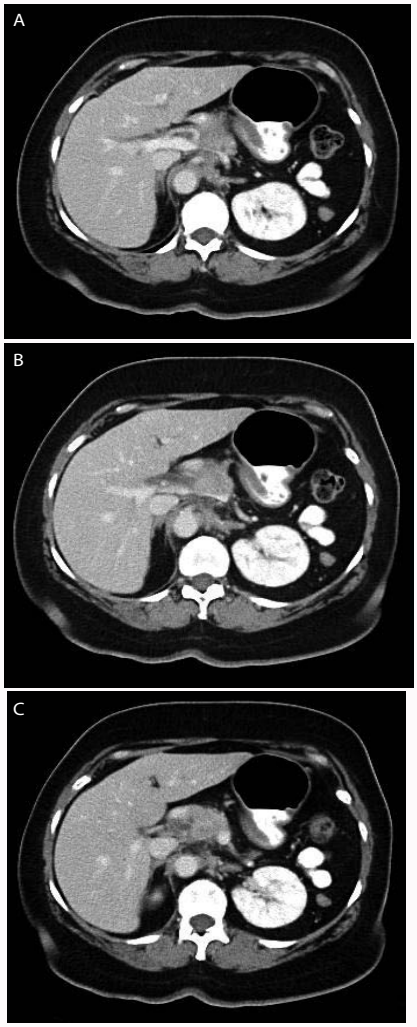

Figure 1: Pre-FOLIFIRINOX (11-15-2014) CT images showing the narrowing of the portal vein, encasement of the celiac axis and involvement of the SMV.

of FOLFIRINOX for two weeks. Once her platelet counts 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 the exploratory laparoscopy, she 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 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 a pancreaticoduodenectomy and superior mesenteric vein reconstruction, there was no palpable pressure gradient across the graft. She was transferred to the surgical intensive

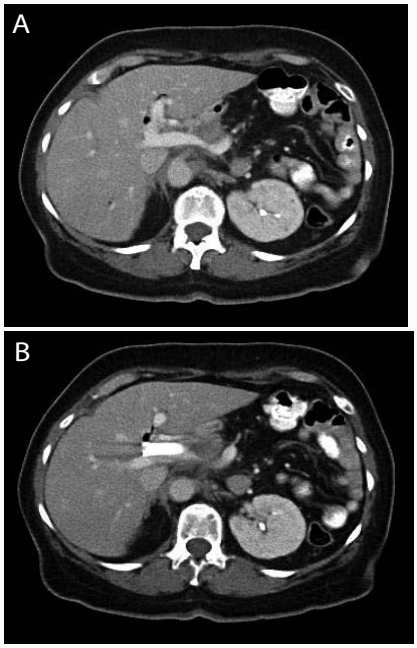

Figure 2: Post-FOLIFIRINOX (11-20-2015) CT images showing (a) a decreased narrowing of the portal vein and (b) a clear fat plane with the tumor regressing from the SMV.

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 a 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 trial 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 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 regimens used for years for colorectal cancer. 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, 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 neoadjuvant 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].

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 also has been associated with liver toxicity. Several studies correlate irinotecan with steatohepatitis [24], suggesting that higher dosages of FOLFIRINOX can increase 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. A2015 patient-level meta-analysis of thirteen FOLFIRINOX studies analyzed in shows that the mean cycle count for those thirteen studies is six cycles. This meta-analysis demonstrates many benefits of FOLFIRINOX, yet the safety of FOLFIRINOX at higher doses is still unknown: no articles have been published that exclusively look at patients with higher cycle counts, specifically patients who have received 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, then guide decisions for neoadjuvant therapy, timing of surgery and resectability.

Conclusion

Oxaliplatin has been correlated with increased risk of sinusoidal obstruction syndrome for colorectal cancer patients. As neoadjuvant 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.

References

1. Conroy T, Desseigne F, Ychou M, Olivier B, Rosine G, Yves B, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. Nejm. 2011; 364: 1817-1825.
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15: 2403-2413.
3. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016; 2045: 1-10.
4. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and Surgical Implications of Neoadjuvant Treatment With FOLFIRINOX for Locally Advanced and Borderline Resectable Pancreatic Cancer. Ann Surg. 2015; 261: 12-17.
5. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol. 2015; 22: 1153-1159.
6. Christians KK, Tsai S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? Oncologist. 2014; 19: 266-274.
7. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol. 2004; 15: 460-466.
8. Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology. 2010; 56: 430-439.
9. Nam SJ, Cho JY, Lee HS, Choe G, Jang JJ, Yoon YS, et al. Chemotherapy-associated hepatopathy in Korean colorectal cancer liver metastasis

patients: Oxaliplatin-based chemotherapy and sinusoidal injury. Korean J Pathol. 2012; 46: 22-29.

10. Robinson S, Wilson C, Burt A, Manas D, White S. Chemotherapy associated liver injury: A systematic review and meta-analysis. Ann Surg Oncol. 2012; 19: 4287-4299.

11. Ryan P, Nanji S, Pollett A, Moore M, Moulton CA, Gallinger S, et al. Chemotherapy-induced liver injury in metastatic colorectal cancer: semiquantitative histologic analysis of 334 resected liver specimens shows that vascular injury but not steatohepatitis is associated with preoperative chemotherapy. Am J Surg Pathol. 2010; 34: 784-791.

12. Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. Preoperative chemotherapy for colorectal liver metastases: Impact on hepatic histology and postoperative outcome. J Gastrointest Surg. 2007; 11: 860-868.

13. Mehta NN, Ravikumar R, Coldham CA, Buckels JAC, Hubscher SG, Bramhall SR, et al. Effect of preoperative chemotherapy on liver resection for colorectal liver metastases. Eur J Surg Oncol. 2008; 34: 782-786.

14. Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol. 2006; 24: 4983-4990.

15. Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg. 2008; 247: 118-124.

16. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008; 371: 1007-1016.

17. Vreuls CP, Driessen A, Olde Damink SW, Koek GH, Duimel H, van den Broek MA, et al. Sinusoidal obstruction syndrome (SOS): A light and electron microscopy study in human liver. Micron. 2016; 84: 17-22.

18. Tajima H, Ohta T, Miyashita T, Nakanuma S, Matoba M, Miyata T, et al. Oxaliplatin-based chemotherapy induces extravasated platelet aggregation in the liver. Mol Clin Oncol. 2015; 3: 555-558.

19. Nalbantoglu IL, Tan BR Jr, Linehan DC, Gao F, Brunt EM. Histological features and severity of oxaliplatin-induced liver injury and clinical associations. J Dig Dis. 2014; 15: 553-560.

20. van den Broek MA, Vreuls CP, Winstanley A, Jansen RL, van Bijnen AA, Dello SA, et al. Hyaluronic Acid as a Marker of Hepatic Sinusoidal Obstruction Syndrome Secondary to Oxaliplatin-Based Chemotherapy in Patients with Colorectal Liver Metastases. Ann Surg Oncol. 2013; 20: 1462-1469.

21. Narita M, Oussoultzoglou E, Chenard MP, Fuchshuber P, Rather M, Rosso E, et al. Liver Injury Due to Chemotherapy-induced Sinusoidal Obstruction Syndrome Is Associated with Sinusoidal Capillarization. Ann Surg Oncol. 2012; 19: 2230-2237.

22. Soubrane O, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, et al. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg. 2010; 251: 454-460.

23. Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol. 2010; 28: 2549-2555.

24. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006; 24: 2065-2072.

25. Marsh RDW, Talamonti MS, Katz MH, Herman JM. Pancreatic cancer and FOLFIRINOX: a new era and new questions. Cancer Med. 2015; 4: 853-863.