ESMO Open
Cancer Horizons

FOLFIRINOX or FOLFOXIRI in locally advanced duodenal adenocarcinoma: are we missing out?

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To cite: Lamarca A, Foster L, Valle JW, *et al*. FOLFIRINOX or FOLFOXIRI in locally advanced duodenal adenocarcinoma: are we missing out? *ESMO Open* 2020;**5**:e000633. doi:10.1136/esmoopen-2019-000633

Received 9 November 2019
Revised 20 December 2019
Accepted 30 January 2020

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Latest cancer statistics in the USA estimate that around 10,590 new cases and 1,590 deaths of small intestinal cancers will be recorded in 2019,[1] which has increased compared with previous statistics (8,070 and 1,150 new cases and deaths were estimated in 2012[2]). Small bowel adenocarcinomas are likely to represent only 40% of all small bowel malignancies[3] and 2% of all gastrointestinal tumours.[4] Unfortunately, prognosis is poor, with around 38% of patients being diagnosed at stages when synchronous metastases are identified; 5-year survival rate is less than 30% and median overall survival is estimated to be around 19 months.[4]

Due to their low incidence, prospective data to inform the most adequate management of small bowel adenocarcinoma is lacking and most treatment recommendations are being based on expert agreement and relying on extrapolated data from colon cancer.[4] This is despite the fact that genomic profiling suggests that small bowel adenocarcinomas are a 'molecularly unique intestinal entity' when compared with counterparts such as colorectal and gastric cancer.[5] In addition, within small bowel adenocarcinomas, duodenal primaries seem to demonstrate genomic aberrations more typical of upper gastrointestinal malignancies such as pancreatic (CDKN2A/B)[6] or gastric cancer (ERBB2/HER2).[7] These findings may explain the worse prognosis and challenging management of duodenal adenocarcinoma compared with other small bowel adenocarcinomas.

In the setting of small bowel adenocarcinoma, duodenal tumours account for around 50% of these. Almost 40% of small bowel adenocarcinoma present with lymph node invasion.[4] Thus, a significant number of patients may present with locally advanced disease, in which scenario, a neoadjuvant approach with systemic chemotherapy could be of interest. Unfortunately, no data for small bowel or duodenal adenocarcinoma exist in this setting and management is extrapolated from other disease groups. In addition, after surgery, the role of adjuvant therapy remains unclear, with ongoing clinical trials exploring its role at the moment (BALLAD trial (NCT02502370)).

The management of advanced small bowel adenocarcinoma is an ongoing challenge. The presence of mismatch repair deficiency may be of relevance with a view to the use of immunotherapy but likely to be present in a small number of patients only. Currently, the most suitable systemic chemotherapy schedule to be used remains unclear. In addition, potential benefit of triple chemotherapy over a doublet combination is not known.

Current treatment recomendations support the use of 'fluoropyrimidine combination, such as 5-FU (5-fluorouracil) or capecitabine with oxaliplatin and cisplatin" or '5-FU with leucovorin if oxaliplatin and cisplatin were contraindicated".[4] The National Comprehensive Cancer Network (NCCN) guidelines suggest triple chemotherapy with 5-FU, oxaliplatin and irinotecan as a treatment option for fit patients with locally advanced or metastatic small bowel adenocarcinoma.[8] The proposed schedule is the one tested in colorectal cancer, so-called FOLFOXIRI[9]; this varies slightly from the triple combination used in advanced pancreatic adenocarcinoma (PDAC) (FOLFIRINOX for metastatic[10] or locally advanced[11] disease) or resected PDAC (modified-FOLFIRINOX[12]) (table 1). The main source of evidence based on which this recommendation is made is the prospective phase II study exploring CAPIRINOX (capecitabine, irinotecan and oxaliplatin) in 33 patients diagnosed with advanced small bowel adenocarcinoma; the achieved radiological objective response rate was 38% (10 patients achieved partial response and 2 complete response).[13] Despite being

Table 1 Triple combination chemotherapy with 5-FU, irinotecan and oxaliplatin in gastrointestinal malignancies

Drug	FOLFOXIRI[9]	FOLFIRINOX[10]	mFOLFIRINOX[12]
Irinotecan	165 mg/m^2 day 1 (2-weekly cycles)	180 mg/m^2 day 1 (2-weekly cycles)	150 mg/m^2 day 1 (2-weekly cycles)
Oxaliplatin	85 mg/m^2 day 1 (2-weekly cycles)	85 mg/m^2 day 1 (2-weekly cycles)	85 mg/m^2 day 1 (2-weekly cycles)
Leucovorin	400 mg/m^2 day 1 (2-weekly cycles)	400 mg/m^2 day 1 (2-weekly cycles)	400 mg/m^2 day 1 (2-weekly cycles)
5-FU bolus	–	400 mg/m^2 day 1 (2-weekly cycles)	–
5-FU infusion	3200 mg/m^2 over 48 hours (2-weekly cycles)	2400 mg/m^2 over 46 hours (2-weekly cycles)	2400 mg/m^2 over 46 hours (2-weekly cycles)

5-FU, 5-fluorouracil; m, modified.

efficacious, the authors concluded that in view of similar progression-free survival and overall survival reported with double chemotherapy, 'the addition of irinotecan does not significantly add to the activity' of a doublet. Unfortunately, no phase III studies have been performed comparing doublet and triple combinations, and publication supporting triple chemotherapy for small bowel adenocarcinoma is scarce, which reflects the fact that even if suggested as an option of treatment for advanced small bowel adenocarcinomas by the NCCN guidelines, it is rarely used in clinical practice.

Triple chemotherapy may be of special interest in scenarios in which downstaging of the disease could impact patients' management, such as the setting of locally advanced disease.[11] While this is an infrequent scenario in colon cancer, it is more common in pancreas, duodenal and rectal tumours due to their anatomic location. Complete pathological responses to triple chemotherapy have been reported but are limited to patients with pancreatic cancer[14–18] and rectal adenocarcinoma,[19] with no reported data for duodenal adenocarcinoma.

Here, we present two cases of patients diagnosed with locally advanced unresectable duodenal adenocarcinoma (cytology/biopsy confirmed) who received FOLFIRINOX chemotherapy in the palliative setting. This schedule was selected based on patients' good Eastern Cooperative Oncology Group (ECOG) performance status (PS) and the fact that FOLFIRINOX had already shown good radiological responses for patients with locally advanced PDAC.[11] In view of reduction in size, both patients were reconsidered for curative resection. In both cases, a complete pathological response was confirmed in the surgical specimen.

The first patient was a 49-year-old man with medical history of treated hepatitis C virus with no other relevant past or family history who presented with gastric outlet obstruction. Endoscopy and computerised tomography (CT) identified a 6 cm mass arising from the second/third portion of the duodenum (figure 1A); endoscopic ultrasound-guided fine needle aspiration confirmed diagnosis of adenocarcinoma (figure 1B). In view of the involvement of superior mesenteric artery (SMA) and vein (SMV), tumour was deemed inoperable (T4N1M0) and the patient started on FOLFIRINOX with palliative aim (ECOG PS 1). Interim CT scan after the first 3 months of chemotherapy showed reduced density and enhancement of duodenal mass; imaging at 6 months confirmed response to therapy with further reduction in size and disappearance of previous solid tissue surrounding the SMA (figure 1C). During this period of time, CA19.9 normalised (990 U/mL at baseline; 23 U/mL when 6 months of FOLFIRINOX was completed). Following discussion in multidisciplinary team meeting (MDT), the patient underwent Whipple resection. The tumour was stented and the duodenum was torn around the stent site during the operation. Microscopic examination of the stented area showed mucosal ulceration and prominent submucosal and muscularis propria fibrosis in keeping with a response to preoperative chemotherapy. No residual carcinoma was identified after extensive blocking of the specimen, indicating a complete pathological response. Thirteen lymph nodes were examined and were free of tumour (ypT0 ypN0) (figure 1D). Five months after surgery, follow-up imaging identified one area of soft tissue in the resection bed. ^{18}F-labelled fluoro-2-deoxyglucose positron emission tomography could not completely exclude tumour recurrence and thus the patient received consolidation treatment with chemoradiotherapy. He is currently free of progression.

The second patient was a 56-year-old woman with no relevant past or family history who presented with iron deficiency anaemia. Endoscopy and CT confirmed a lesion in the duodenum involving second and third portions of the duodenum. Biopsies taken at the time of endoscopy confirmed moderately differentiated adenocarcinoma. Even though there was no evidence of SMA and SMV involvement, tumour was deemed locally advanced (T4N1M0) with attenuation/occlusion of the splenic vein and splenic artery, extension of the duodenal mass into the aorta and the distal pancreatic body and presence of upper lymphadenopathy in the aortocaval region. Chemotherapy with FOLFIRINOX was started (ECOG PS 1); unfortunately, after the first cycle, the patient developed duodenal obstruction, requiring admission for duodenal stenting. Once this was resolved, chemotherapy was recommenced. After the first 3 months of chemotherapy, CT showed a reduction in size of the duodenal mass with reduction of the fat stranding around the tumour; the case was rediscussed in the MDT and agreed to proceed with a pancreas-sparing duodenectomy. Pathology assessment of the resected specimen showed changes in keeping with chemotherapy effect, with

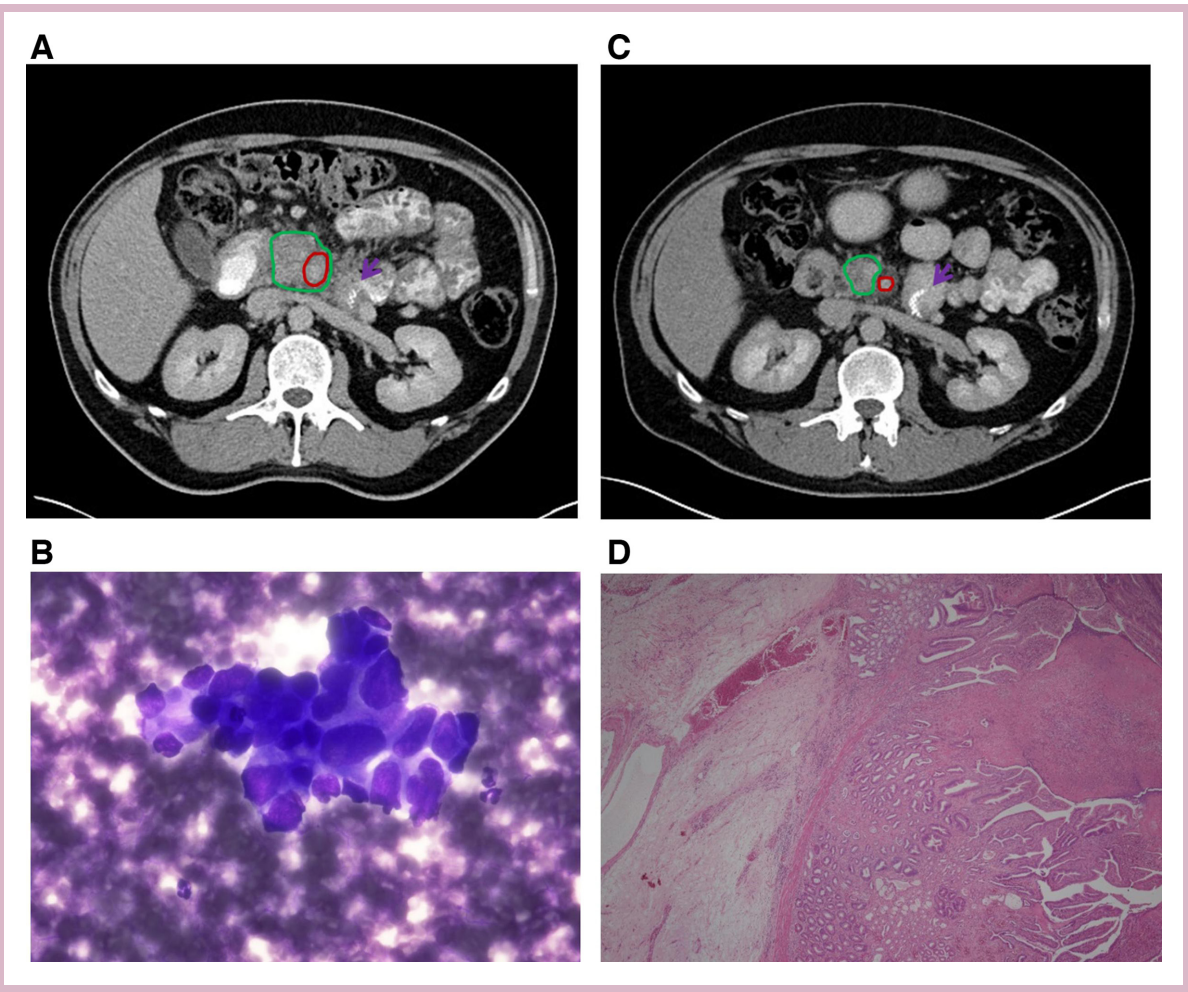

Figure 1 Summary of radiological and pathology findings before and after FOLFIRINOX chemotherapy (case 1). (A) CT scan showed primary tumour arising from the duodenum (green), locally advanced and unresectable in view of superior mesenteric artery (SMA) involvement (red); presence of duodenal stent (purple arrow). (B) Pre-chemotherapy biopsy confirmed diagnosis of adenocarcinoma. (C) After 6 months of FOLFIRINOX chemotherapy, CT confirmed reduction in size of the primary tumour (green), with cuff of tissue surrounding the SMA being less solid in appearance (red) and not infiltrated by tumour; duodenal stent still in situ (purple arrow). (D) Complete pathological response was identified in Whipple resection specimen with no evidence of residual disease.

no evidence of residual tumour. Two aortic lymph nodes were tumour-free but also contained large areas of fibrosis, suggesting response to chemotherapy. Patient has been 13 months free of disease and continues on follow-up.

To the best of our knowledge, this is the first time that complete pathological responses to triple chemotherapy in locally advanced duodenal adenocarcinoma have been reported, while other reports are available with doublet combinations[20] or in patients with metastatic disease.[21] As summarised above, evidence guiding the treatment of advanced small bowel adenocarcinoma is lacking, with most data being extrapolated from lower gastrointestinal tract tumours. These two cases show that FOLFIRINOX is an effective treatment for duodenal adenocarcinoma and that its use should be considered for fit patients, especially in the setting of locally advanced disease in view of its potential to downstage the disease. Triple combinations have not been explored much in small bowel adenocarcinoma due to similar efficacy data to the one achieved with doublets[13]; even though this may be fair in the metastatic scenario, we may be losing a useful combination for patients with locally advanced disease. We believe that the role of triple chemotherapy in the form of FOLFIRINOX or FOLFOXIRI should be further explored in the setting of prospective clinical trials focused on patients with locally advanced duodenal adenocarcinoma.

Contributors All authors contributed to the writing of the manuscript.

Funding AL received funding from The Christie Charity.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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