Clinical Case Report

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Anti epidermal growth factor receptor therapy in small bowel adenocarcinoma

Case report and literature review

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Abstract

Rationale: Small bowel adenocarcinoma (SBA) is an uncommon gastrointestinal cancer, thus limited data about treatment for advanced disease are available. The lack of specific guidelines has justified the use of therapeutic protocols usually applied in advanced colorectal cancer. Few and preliminary data have suggested possible clinical benefit from the use of target therapy such as bevacizumab and cetuximab.

Patient concerns: We present the case of a young woman who was admitted to the emergency department for acute abdominal pain, nausea, and vomiting related to a jejunal stenosis.

Diagnoses: An enteroscopy with jejunal biopsy showed poorly differentiated cancerous cells suggestive for primary intestinal cancer. There were no signs of metastatic disease at radiological evaluation. A jejunal resection was subsequently carried out and the diagnosis of mucinous adenocarcinoma of the jejunum was confirmed.

Interventions: The computed tomography scan performed 1 month after surgery showed metastatic disease. Therefore, the patient received combined protocols of chemotherapy and either bevacizumab or the anti-epidermal growth factor receptor (EGFR) panitumumab.

Outcomes: A partial response (PR) was achieved with Folfox plus panitumumab and a maintenance therapy with panitumumab is being conducted with a mild toxicity and a progression free survival of 19 months since the beginning of panitumumab.

Lessons: This is, to the best of our knowledge, the first report in the literature of a patient with SBA who has benefitted from panitumumab with an overall survival of 83 months.

Abbreviations: CRC = colorectal cancer, EGFR = epidermal growth factor receptor, PR = partial response, SBA = small bowel adenocarcinoma, VEGF = vascular endothelial growth factor.

Keywords: jejunum, panitumumab, small bowel adenocarcinoma, target therapy

1. Introduction

Small bowel adenocarcinoma (SBA), which accounts for about one-third of all cancers of the small bowel, is considered a rare tumor. The majority of SBA develops sporadically though some genetic conditions such as Lynch syndrome, familial adenomatous polyposis, and Peutz-Jeghers syndrome cause an increased risk of the disease. There is a slight male predominance and the duodenum is the most common tumor site. Unlike BRAF mutations, which are uncommon in sporadic SBA, the rate of K-ras mutations, as high as 40% to 60%, resembles that of colorectal cancer (CRC).[1] Conversely, the presence of microsatellite instability, which is reported up to 35%, is more frequent than that reported in CRC. Clinical studies regarding systemic treatment of advanced SBA are limited.[2–5] The lack of high-level data has prevented from writing practical guidelines. Based on either retrospective or phase-2 studies, the combination of fluoropyrimidines and oxaliplatin is regarded as the standard regimen for advanced and metastatic disease.[2,3] Because in tissue microarrays of SBA a high percentage of expression of both epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) was demonstrated, a possible benefit from therapeutic strategies targeting EGFR and VEGF receptor is expected to be.[6] Nonetheless, the use of target therapy has been rarely investigated, testified by only a few case reports and 3 clinical studies (Table 1). Within the context of anti-EGFR therapy, to the best of our knowledge, only 2 experiences referred to chemotherapy associated with cetuximab.[10,11] Here, the case of a patient, who received a combination of chemotherapy and the monoclonal antibody panitumumab for a jejunal adenocarcinoma, is described.

2. Case report

The case concerns a 47-year-old female patient with a previous diagnosis of celiac disease and a long history of Hashimoto thyroiditis requiring thyroid hormone replacement therapy. On December 2010, the patient was admitted to the emergency

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Ethical approval was not necessary because we are dealing with a case report.

Informed consent was obtained but we are not asked to provide it because we didn't use photographs or video concerning the patient and we are obliged to protect patient privacy.

Conflict of interest: None declared.

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Table 1

Case series of advanced SBA treated with biologic agents.

Reference	Type study	Cancer site (N patients)	Mutational status	Treatment	Line	Maximal toxicity	Outcomes
Clinical studies with chemotherapy and target agents in advanced SBA							
Gulhati et al[7]	Phase-2, single arm	SBA, AAC (30)	–	CAPOX + BEV	1st	Fatigue G3 (23%) Hypertension G3 (23%) Neutropenia G3 (20%) Diarrhea G3 (10%)	ORR: 48.3% PFS: 8.7 mo OS: 12.9 mo
Aydin et al[8]	Retrospective (2 groups: A–B)	SBA (28)	–	CHEMO + BEV(A) CHEMO(B)	1st	Hematologic G3 (A: 25%, B: 6%)	ORR (A–B): 58.3–43.7% (p: 0.44) PFS (A–B): 9.6–7.7 mo (p: 0.48) OS (A–B): 18.5–14.8 mo (p: 0.73)
Takayoshi et al[9]	Retrospective (2 groups: A–B)	SBA, AAC (33)	K-ras, Her2-neu	CHEMO + BEV(A) CHEMOalone-CHEMO + CET(B)	1st, 2nd, 3rd	–	OS (A–B): 21.9–11.4 mo (p: 0.18)
Case series of advanced SBA treated with chemotherapy plus target agents							
Santini et al[10]	Case series	Duodenum (2) Jejunum (2)	WT K-ras (3)	CET + IRI based CHEMO	1st (2) 2nd (2)	Neutropenia G3 Diarrhea G3 Rash G2	OS: 35, 19, 7*, 17* mo
De Dosso et al[11]	Case report	Ileum	WT K-ras	CET + IRI	3rd	Rash G2	OS: 27 mo
Tsang et al[12]	Case report	Jejunum	–	GEM + OXA + BEV	1st	–	OS: 12* mo
Nagaraj et al[13]	Case report	Duodenum	–	FOLFOX + BEV	1st	–	OS: 96* mo

AAC = ampullary adenocarcinoma, BEV = bevacizumab, CET = cetuximab, CHEMO = chemotherapy, GEM = gemcitabine, IRI = irinotecan, mo = months, ORR = overall response rate, OS = overall survival, OXA = oxaliplatin, PFS = progression free survival, SBA = small bowel adenocarcinoma, WT = wilde type.

* Still alive at publication time.

department for acute abdominal pain, nausea, and vomiting related to an intestinal obstruction. A computed tomography (CT) scan revealed a severe jejunal stenosis without other pathologic findings. An enteroscopy with jejunal biopsy showed poorly differentiated cancerous cells suggestive for primary intestinal cancer. A jejunal resection was subsequently carried out and the diagnosis of mucinous adenocarcinoma of the jejunum confirmed: pT4 pN1 (1/13) G3 V1 R0, Stadium IIIA sec AJCC 2010. Immunohistochemistry for mismatch repair markers MLH-1 and MSH-2 was normal. A postoperative CT scan, performed 1 month after surgery, revealed peritoneal carcinomatosis and abdominal lymph nodes. Thus, first-line chemotherapy with 5-fluorouracil plus oxaliplatin (FOLFOX) plus bevacizumab was delivered for a year with stable disease as the best response. According to common terminology criteria for adverse events toxicity criteria, G1 hypertension and G2 nausea were reported. Bevacizumab alone was continued for further 5 months, until August 2012, when a CT scan showed a fast growing left pelvic mass ($14 \times 13 \times 18$ cm), which showed increased glucose uptake at 18-f fdg positron emission tomography/computed tomography (PET/CT). Patient underwent a palliative resection of the mass. Histology confirmed the small bowel origin of the tumor and showed wilde type (wt) of both K-ras (codons 12 et 13) and BRAF genes. After a holiday treatment period of 30 months, during which the patient retained a good performance status along with stable radiologic features, on March 2015, a CT scan revealed the appearance of a further interaortocaval adenophathy. On account of the disease oligo-progression, it was decided not to use conventional-dose chemotherapy but enroll the patient in an experimental protocol based on metronomic capecitabine and proton pump inhibitors.[14,15] During the study period she also received stereotactic radiotherapy on the growing abdominal adenophathies. The experimental treatment was continued for 8 months until February 2016, when a 18-f fdg PET/CT scan showed progressive disease in lung, infradiaphragmatic, and supradiaphragmatic lymph nodes. Based on both good performance status and response to first line chemotherapy, a rechallenge with FOLFOX combined with panitumumab was decided according to the Kras status. Three months later a partial response was documented. Oxaliplatin was discontinued after 6 cycles of treatment for the occurrence of gastrointestinal toxicity up to G3. Moreover, because of G3 follicular skin rash, panitumumab was reduced to 80% of the full dose. Since then, a maintenance capecitabine (625 mg/mq bid die, continuously) and panitumumab therapy is ongoing, with a duration of 15 months. Both skin rash and mucosistis of G1 are the only toxicities following this maintenance treatment while the last 18-f fdg PET/CT has confirmed a partial response. Overall survival has by now reached 83 months from the diagnosis.

3. Discussion

Few small prospective phase-2 studies have directly tested chemotherapy in patients affected with advanced SBA.[2–5] Oxaliplatin in combination with either 5-fluorouracil or capecitabine is commonly used in the frontline setting.[2,3] The combination of mitomycin C, doxorubicin, and 5-fluorouracil has showed minimal efficacy[4] and it is not usually employed. A combination of 5-fluorouracil and irinotecan (FOLFIRI) regimen was evaluated retrospectively as second line therapy after failure of first line platinum-based chemotherapy, but results were modest.[16] Recently, following the survival benefit reached with the use of drug triplets in both CRC and pancreatic cancer, the North Central Cancer Treatment Group performed the first pharmacogenetic-based phase-2 study (N0543) in patients with advanced untreated SBA, using a genotype-dosed combination of capecitabine, irinotecan, and oxaliplatin.[5] Although the toxicity profile seemed

Table 2

Clinical trials with target therapy for advanced SBA.

Trial code	Study design	Setting	Protocol	Status
NCT01202409	II, not R	WT K-ras SBA, AAC	PAN	Ongoing, not recruiting
NCT01208103	II, not R	SBA, AAC	CAP + OXA + BEV	Ongoing, not recruiting
NCT03108131	II, not R	RT	COB + ATE	Recruiting
NCT02034110	II, not R	BRAF V600E mutated RT	DAB + TRA	Recruiting
NCT03095781	I, not R	GIC	PEM + XL888	Not yet open
NCT00987766	I, not R	BPC, DC, AAC	ERL + GEM + OXA	Ongoing, not recruiting
NCT00005842	I, not R	A/M C	TIP + TRAS	Completed
NCT00397384	I, not R	GIC, HNC, NSCLC	CET + ERL	Completed

A/M C = advanced/metastatic cancer, AAC = ampullary adenocarcinoma, ATE = Atezolizumab, BEV = Bevacizumab, BPC = bilio-pancreatic cancer, CAP = Capecitabine, CET = Cetuximab, COB = Cobimetinib, DAB = Dabrafenib, DC = duodenal cancer, ERL = Erlotinib, GEM = Gemcitabine, GIC = gastrintestinal cancer, HNC = head and neck cancer, NSCLC = non small cell lung cancer, OXA = Oxaliplatin, PAN = Panitumumab, PEM = Pembrolizumab, R = randomized, RT = rare tumors, TIP = Tipifarnib, TRA = Trametinib, TRAS = Trastuzumab, XL888 = inhibitor of HSP90.

to be favorable, conclusions about benefits of the addition of irinotecan to oxaliplatin and fluorouracil could not be achieved. The lack of clinical studies due to the rarity of SBA has implied for the therapeutic decision-making the adoption of clinical guidelines created for large bowel adenocarcinoma. Although combination treatments with bevacizumab have generated encouraging results, no conclusion can be drawn at present. Indeed, the interpretation of data should consider the following remarks: small sample of patients included, heterogeneity of the study population (SBA with or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-SOX) used with bevacizumab and finally, variability of patients set.[7–9] Even a lower level of evidence supports the option of an anti-EGFR therapy. In fact, only few patients affected with SBA received cetuximab while none was treated with panitumumab until now.[10,11] These monoclonal antibodies, alone or combined with chemotherapy, are widely adopted for the treatment of patients with wild-type RAt Sarcoma (RAS) metastatic CRC. However, very limited data pertain the use of maintenance anti-EGFR therapy.[17] The present case referred to a patient affected with wt RAS, metastatic SBA who obtained both partial response and a long progression free survival (PFS) following an induction therapy with FOLFOX and panitumumab. A maintenance regimen with fluoropyrimidine and anti-EGFR antibody was started and carried out with a good tolerability. To the best of our knowledge no other similar experience has been presented up to now.

4. Conclusion

The use of chemotherapy in SBA is solely supported by level II evidence. For such reason, anticancer regimens suitable for CRC are usually applied. Furthermore, just anecdotal experiences about the use of anti-EGFR monoclonal antibodies have been reported. Although some clinical trials are ongoing to test target therapies in advanced or metastatic SBA (Table 2), there is the need of further comparative studies aimed at better define therapy of this orphan disease.

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References

[1] Zaaimi Y, Aparicio T, Laurent-Puig P, et al. Advanced small bowel adenocarcinoma: Molecular characteristics and therapeutic perspectives. Clin Res Hepatol Gastroenterol 2016;40:154–60.

[2] Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of vater. J Clin Oncol 2009;27:2598–603.

[3] Xiang XJ, Liu YW, Zhang L, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anticancer Drugs 2012;23:561–6.

[4] Gibson MK, Holcroft CA, Kvols LK, et al. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. Oncologist 2005;10:132–7.

[5] McWilliams RR, Foster NR, Mahoney MR, et al. North Central Cancer Treatment Group N0543 (Alliance): a phase 2 trial of pharmacogenetic-based dosing of irinotecan, oxaliplatin, and capecitabine as first-line therapy for patients with advanced small bowel adenocarcinoma. Cancer 2017;123:3494–501.

[6] Overman MJ, Pozadzides J, Kopetz S, et al. Immunophenotype and molecular characterisation of adenocarcinoma of the small intestine. Br J Cancer 2010;102:144–50.

[7] Gulhati P, Raghav K, Shroff RT, et al. Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of vater: a single-center, open-label, phase 2 study. Cancer 2017;123:1011–7.

[8] Aydin D, Sendur MA, Kefeli U, et al. Evaluation of bevacizumab in advanced small bowel adenocarcinoma. Clin Colorectal Cancer 2017;16:78–83.

[9] Takayoshi K, Kusaba H, Uenomachi M, et al. Suggestion of added value by bevacizumab to chemotherapy in patients with unresectable or recurrent small bowel cancer. Cancer Chemother Pharmacol 2017;80:333–42.

[10] Santini D, Fratto ME, Spoto C, et al. Cetuximab in small bowel adenocarcinoma: a new friend? Br J Cancer 2010;103:1305.

[11] De Dosso S, Molinari F, Martin V, et al. Molecular characterisation and cetuximab-based treatment in a patient with refractory small bowel adenocarcinoma. Gut 2010;59:1587–8.

[12] Tsang H, Yau T, Khong PL, et al. Bevacizumab-based therapy for advanced small bowel adenocarcinoma. Gut 2008;57:1631–2.

[13] Nagaraj G, Zarbalian Y, Flora K, et al. Complete response and prolonged disease-free survival in a patient with recurrent duodenal adenocarcinoma treated with bevacizumab plus FOLFOX6. J Gastrointest Oncol 2014;5:E1–6.

[14] Marchetti P, Milano A, D'Antonio C, et al. Association between proton pump inhibitors and metronomic capecitabine as salvage treatment for patients with advanced gastrointestinal tumors: a randomized phase II trial. Clin Colorectal Cancer 2016;15:377–80.

[15] Falcone R, Roberto M, D'Antonio C, et al. High-doses of proton pump inhibitors in refractory gastro-intestinal cancer: a case series and the state of art. Dig Liver Dis 2016;48:1503–5.

[16] Zaanan A, Gauthier M, Malka D, et al. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer 2011;117:1422–8.

[17] García Alfonso P, Benavides M, Sánchez Ruiz A, et al. Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (S/A) C as maintenance therapy in patients (P) with metastatic colorectal cancer (mCRC): The MACRO-2 trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). Ann Oncol 2014;25(Suppl):iv168abstr 499O.