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 carcinoma. 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
Clinical studies with chemotherapy and target agents in advanced SBA

A jejunal resection was subsequently carried out and the differentiated cancerous cells suggestive for primary intestinal 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 fluid collection. A CT scan was performed for acute abdominal pain, nausea, and vomiting. The 23 year-old was still alive at publication time.

Table 1
Case series of advanced SBA treated with biologic agents.

| Reference | Type study | Cancer site | Mutational status | Treatment | Line | Maximal toxicity | Outcomes |
|-----------|------------|-------------|-------------------|-----------|------|------------------|----------|
| Clinical studies with chemotherapy and target agents in advanced SBA | Phase-2, single arm | SBA, AAC (30) | – | CAPOX + BEV | 1st | – | ORR: 48.3% |
| Gulhati et al[7] | Retrospective (2 groups: A–B) | SBA (28) | – | CHEMO + BEV(A) | 1st | Hematologic G3 (A: 25%, B: 6%) | OS (A–B): 8.7–12.9 mo |
| Aydin et al[8] | Retrospective (2 groups: A–B) | SBA, AAC (33) | K-ras, Her2-neu | CHEMO + BEV(A) | 1st, 2nd, 3rd | – | OS (A–B): 21.9–11.4 mo |
| Santini et al[9] | Case series | Duodenum (2) | WT K-ras (3) | CHEMOCetuximab-chemo | 2nd (2) | Neutropenia G3 | OS: 35, 19, 7*, 17* mo |
| Tsang et al[10] | Case report | Jejunum (2) | – | CHEMOCetuximab-chemo | 2nd (2) | Diarrhea G3 | OS (A–B): 21.9–11.4 mo |
| De Dosso et al[11] | Case report | Jejunum (2) | – | CHEMOCetuximab-chemo | 2nd (2) | Rash G2 | OS: 27 mo |
| Nagaraj et al[12] | Case report | Jejunum (2) | – | CHEMOCetuximab-chemo | 2nd (2) | Rash G2 | OS: 12* 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 = wild type. *Still alive at publication time.

3. Discussion

Few small prospective phase-2 studies have directly tested chemotherapy in patients affected with advanced SBA[2, 3, 4, 5]. Oxaliplatin in combination with either 5-fluorouracil or capetitabine is commonly used in the frontline setting. Two of these studies[6, 7] have 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 capetitabine, irinotecan, and oxaliplatin.[8] Although the toxicity profile seemed
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-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without ampullary adenocarcinoma), nature of the study, different chemotherapy protocols (FOLFOX-FOLFIRI-CAPOX-or without am

### 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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## Table 2

| 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 |
| NCT02634110 | 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 |
| NCT00305842 | I, not R | A/M C | TIP + TRAS | Completed |
| NCT00307384 | I, not R | GIC, HNC, NSQLC | CET + ERL | Completed |