Capecitabine-Associated Terminal Ileitis

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Abstract
Capecitabine is an oral fluoropyrimidine used as adjuvant and palliative chemotherapy in patients with colorectal cancer. Diarrhea is a well-known side effect of capecitabine and 5-fluorouracil agents. We present a case with terminal ileitis as a rare adverse event of capecitabine treatment. Capecitabine-induced terminal ileitis is likely to be underreported. It should be considered more often as a cause of severe and atypical complaints of diarrhea during treatment with capecitabine or other 5-fluorouracil agents.

Introduction

Capecitabine is an oral fluoropyrimidine, which is the chemotherapy backbone in adjuvant and palliative systemic treatment in patients with colorectal cancer. Gastrointestinal adverse events are common during capecitabine treatment, mostly consisting of nausea and diarrhea. In this paper, we present a rare case of capecitabine-associated terminal ileitis.
Case Report

A 69-year-old woman without any comorbidities underwent a sigmoid resection for an adenocarcinoma of the sigmoid colon (pT3N2). According to the Dutch guidelines, adjuvant chemotherapy was started 5 weeks after surgery with CAPOX, consisting of capecitabine and oxaliplatin every 3 weeks. Before start, dihydropyrimidine dehydrogenase genotype testing was performed without signs of DPD deficiency.

Shortly after the start of chemotherapy, she had complaints of nausea and a reduced appetite. After 2 weeks, she developed watery stools (without blood) twice daily. The diarrhea worsened to 4–6 times daily during the following days at which loperamide was administered. Three weeks after the start of chemotherapy, she was hospitalized. Physical examination revealed a moderately ill patient with normal vital functions. No abnormalities were found on examination of the heart and the lungs. Upon examination of the abdomen, lively bowel sounds were found, and the abdomen was distended but not tender at palpation. Digital rectal examination revealed no abnormalities. Also, examination of the skin and extremities showed no abnormalities.

The laboratory results showed a hemoglobin level of 8.3 mmol/L (reference 7.5–10.0), thrombocytes 300/nL (reference 150–400), leukocytes 6.0/nL (reference 4.0–10.0), and a C-reactive protein of 83 mg/L (reference <6), with normal liver biochemistry and kidney function. The following days, the diarrhea worsened to a frequency of 12 times a day, and intravenous fluids were administered. Stool cultures were negative for pathogenic bacteria and protozoa. A colonoscopy with biopsy showed an ileitis with superficial but extensive ulceration in the terminal ileum (Fig. 1). Magnetic resonance enterography showed a 5-mm wall thickening of the terminal ileum over a distance of more than 15 cm. More proximal in the ileum, a second area of wall thickness was found over a distance of 7 cm. We discontinued the CAPOX treatment and started budesonide 9 mg once daily. The diarrhea and nausea decreased in the following weeks. After 4 weeks of budesonide use, adjuvant treatment was continued with FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) every 2 weeks. The complaints of nausea and diarrhea resumed mildly (grade 1) during FOLFOX therapy, and therefore we continued budesonide. After 3 cycles of FOLFOX, she decided to discontinue the adjuvant treatment because she was suffering from a vital depression. The budesonide was discontinued after cessation of the chemotherapy without signs of recurrence of ileitis.

Discussion

Diarrhea is a well-known, dose-dependent side effect of the treatment with capecitabine. The diarrhea usually starts at the end of the second or in the third week, is mostly mild, recovers after a few days with sometimes a necessity of treatment with anti-motility agents such as loperamide. Grade 3–4 diarrhea occurs in 11.4% of patients treated with capecitabine monotherapy [1]. In contrast, in patients with a DPD deficiency the diarrhea starts often within the first week and is life threatening [2].

Oxaliplatin can also cause diarrhea but typically starts early after administration within 3–4 days and resolves after 1–2 days without any intervention. In patients treated with the
combination of capecitabine and oxaliplatin, grade 3–4 diarrhea occurs in approximately 18% of cases [1, 3].

Capecitabine-induced diarrhea is caused by acute injury to the intestinal mucosa, which leads to loss of the epithelium [4]. By inducing a mitotic arrest of the crypt cells, the ratio of immature secretory crypt cells to mature villous enterocytes increases, leading to a higher volume of fluid leaving the small bowel that goes beyond the absorptive capacity of the colon, causing clinically significant diarrhea [4, 5].

In the current case, the complaints of diarrhea started within 2 weeks after the first administration of chemotherapy and worsened over time, needing further diagnostic tests, which revealed a terminal ileitis. Terminal ileitis has been previously reported in 8 cases (Table 1) [6–11]. Yet, the pathophysiology and the management of capecitabine-induced terminal ileitis remain unclear. Of the 9 reported cases, all received intravenous fluids, 2 received parenteral nutrition and 7 received antibiotics. Our patient was the only one treated with steroids. Because steroids seem to be contra-indicated in case of mucositis, we believe steroids should be given only after performing colonoscopy with biopsy revealing a clear diagnosis of ileitis.

Considering the cancer treatment, in 5 cases capecitabine was permanently discontinued; in 2 of these cases, a different type of chemotherapy was started, and in 3 cases no chemotherapy was resumed at all. In none of the cases was capecitabine re-administered at the same dose; in 2 cases, capecitabine was restarted at a reduced dose, and in 1 case capecitabine was replaced by 5-fluorouracil (FOLFOX).

If continuation of treatment is desired, patient and tumor characteristics should be taken into account. In a palliative setting, toxicity is an important factor influencing quality of life. Therefore, in case of capecitabine-induced terminal ileitis, resuming capecitabine in a palliative setting seems to be an inconsistent decision. In an adjuvant setting, the absolute risk reduction of relapse has to be weighted against the risk of toxicity. Hence, a re-challenge with a dose reduction of capecitabine or other 5-fluorouracil agents might be a valid option.

An alternative treatment option could be S1, which is an oral fluoropyrimidine only registered for use in a palliative setting that includes three different agents: tegafur, gimeracil, and oteracil. S1 is associated with a significantly lower incidence of hand-foot syndrome compared with capecitabine, with comparable efficacy [12].

Another oral cytotoxic agent named trifluridine-tipiracil (TAS-102) is an oral fluoropyrimidine with a different mechanism of action, which is registered for patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapy [13, 14]. Trifluridine is a thymidine-based nucleic acid analogue; the triphosphate form of trifluridine interferes with DNA synthesis and inhibits cell proliferation. Tipiracil is a potent thymidine phosphorylase inhibitor, which prevents the rapid degradation of trifluridine, resulting in an increased trifluridine exposure [14]. Its associated toxicities are gastrointestinal and hematologic, but in contrast to capecitabine, the gastrointestinal toxicities with trifluridine-tipiracil were almost all grade 1 and 2 with only few grade ≥3 events [13, 14].
Conclusion

Terminal ileitis should be considered more often when the pattern of diarrhea and other complaints are not typical for capecitabine-induced mucositis. Continuing chemotherapy treatment with alternative fluoropyrimidines is an option.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have nothing to disclose.

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Fig. 1. Diagnostic findings.  

1. Terminal ileitis at colonoscopy.  
2. Extensive inflammation of the small intestine at pathological review of the biopsy.  
3. MR enterography showing a distention of the colon and thickening of the terminal ileal loop (arrow).
Table 1. Earlier reports on capecitabine-associated terminal ileitis

| First author [Ref.], year | Patient | Oncologic treatment | Clinical description | Diagnostic findings | Acute management | Anticancer treatment |
|---------------------------|---------|--------------------|----------------------|---------------------|-----------------|---------------------|
| 1 Radwan [6], 2012        | Male    | 67 years           | Colon carcinoma      | After cycle 2:      | CT scan:         | Intravenous fluids  | Capecitabine        |
|                           |         | Adjuvant           |                      | Diarrhea Lower      | suggestive of    | Antibiotics         | permanently         |
|                           |         | Capecitabine       |                      | abdominal discomfort| acute ileitis    |                     | discontinued        |
|                           |         |                    |                      | Reduced appetite    | DPyD: unknown   |                     | No further          |
|                           |         |                    |                      |                     |                 |                     | chemotherapy        |
|                           |         |                    |                      |                     |                 |                     | was started         |
| 2 Barton [7], 2006        | Male    | 54 years           | Colon carcinoma      | After cycle 3:      | Stool cultures:  | Parenteral nutrition| Unknown             |
|                           |         | Adjuvant           |                      | Diarrhea Abdominal  | negative         |                     |                     |
|                           |         | Capecitabine       |                      | cramps              | Colonoscopy:     |                     |                     |
|                           |         |                    |                      |                     | ulcerative ileitis|                     |                     |
|                           |         |                    |                      |                     | with eosinophilic|                     |                     |
|                           |         |                    |                      |                     | infiltrates      |                     |                     |
|                           |         |                    |                      |                     | DPyD: unknown    |                     |                     |
| 3 Bouna [8], 2011         | Male    | 73 years           | Colon cancer with    | After cycle 3:      | CT scan:         | Intravenous fluids  | Capecitabine        |
|                           |         | Palliative         | liver metastases     | Diarrhea Nausea     | circumferential  | Antibiotics         | oxaliplatin and     |
|                           |         | Capecitabine       |                      | Abdominal pain      | edema of the     |                     | bevacizumab         |
|                           |         | Oxaliplatin        |                      | Fever               | terminal ileum   |                     | continued at a      |
|                           |         |                    |                      |                     | suggestive of     |                     | reduced dose        |
|                           |         | Bevacizumab        |                      | acute ileitis       | acute ileitis    |                     |                     |
|                           |         |                    |                      |                     | DPyD: not tested |                     |                     |
| 4 Al-Gahmi [9], 2012      | Male    | 65 years           | Metastatic rectum    | After 12 days:      | Colonoscopy:     | Intravenous fluids  | Capecitabine was    |
|                           |         | Palliative         | carcinoma            | Diarrhea Abdominal  | isolated ulceration| Antibiotics         | permanently         |
|                           |         | Capecitabine       |                      | pain Fever Emeis    | of the terminal   |                     | discontinued        |
|                           |         | Oxaliplatin        |                      |                     | ileum with       |                     | Treatment with      |
|                           |         |                    |                      |                     | eosinophilic     |                     | exemestane and      |
|                           |         |                    |                      |                     | infiltrates      |                     | everolimus was      |
|                           |         |                    |                      |                     | DPyD: no mutation|                     | started 4 months    |
|                           |         |                    |                      |                     |                 |                     | later               |
| 5 Mokrim [10], 2014       | Female  | 66 years           | Metastatic breast    | After 14 days:      | Stool cultures:  | Intravenous fluids  | Capecitabine        |
|                           |         | Palliative         | cancer                | Diarrhea Fever      | negative         | Antibiotics         | permanently         |
|                           |         | Capecitabine       |                      | Emeis               | CT scan: submucosal|                     | discontinued        |
|                           |         |                    |                      |                     | edema of the      |                     | Treatment with      |
|                           |         |                    |                      |                     | distal ileum with |                     | exemestane and      |
|                           |         |                    |                      |                     | abnormal          |                     | everolimus was      |
|                           |         |                    |                      |                     | thickening of its |                     | started 4 months    |
|                           |         |                    |                      |                     | wall Colonoscopy |                     | later               |
|                           |         |                    |                      |                     | with biopsy:     |                     |                     |
|                           |         |                    |                      |                     | inflammatory      |                     |                     |
|                           |         |                    |                      |                     | changes in the    |                     |                     |
|                           |         |                    |                      |                     | ileal mucosa      |                     |                     |
|                           |         |                    |                      |                     | DPyD: mutation    |                     |                     |
|                           |         |                    |                      |                     | DPYD*5,6         |                     |                     |
| 6 Mokrim [10], 2014       | Female  | 67 years           | Metastatic breast    | After cycle 2:      | Stool cultures:  | Intravenous fluids  | Capecitabine        |
|                           |         | Palliative         | cancer                | Diarrhea Fever      | negative         | Antibiotics         | permanently         |
|                           |         | Capecitabine       |                      | Reduced appetite    | CT scan: partial|                     | discontinued        |
|                           |         |                    |                      | Fatigue             | thickening of the|                     |                     |
|                           |         |                    |                      |                     | terminal ileal    |                     |                     |
|                           |         |                    |                      |                     | loop DPyD: no     |                     |                     |
|                           |         |                    |                      |                     | mutation          |                     |                     |
| 7 Lee [11], 2015          | Female  | 61 years           | Colon cancer with    | After cycle 4:      | CT scan:         | Intravenous fluids  | One week after      |
|                           |         | Palliative         | liver/jung           | abdominal pain right| extensive         | Antibiotics         | discharge, irinotecan|
|                           |         | Capecitabine-     | metastases           | lower quadrant      | submucosal edema  | G-CSF               | and bevacizumab were |
|                           |         | irinotecan-        |                      | Diarrhea Vomiting    | at the terminal   |                     | resumed Capcitabine  |
|                           |         | bevacizumab        |                      | Fever               | middle and        |                     | was permanently      |
|                           |         |                    |                      |                     | part of the ileum |                     | discontinued        |
|                           |         |                    |                      |                     | DPyD mutation:    |                     |                     |
|                           |         |                    |                      |                     | unknown           |                     |                     |
| 8 Lee [11], 2015          | Female  | 59 years           | Metastatic colon     | After start,       | CT scan:         | ICU admission       | Capecitabine was     |
|                           |         | Palliative         | cancer                | diarrhea grade 1,   | diffuse submucosal| Total parenteral    | permanently         |
|                           |         | Capecitabine       |                      | after 3th cycle     | edema in a long  | nutrition           | discontinued        |
|                           |         |                    |                      | sudden worsening    | segment of the    | Inotropic support   |                     |
|                           |         |                    |                      | of diarrhea (grade 4)| distal ileum to   | Electrolyte        |                     |
|                           |         |                    |                      | and mucositis (grade 3) | terminal ileum | replacement         |                     |
|                           |         |                    |                      |                     | DPyD mutation:   |                     |                     |
|                           |         |                    |                      |                     | unknown           |                     |                     |
| 9 Van Hellemond, 2018      | Female  | 69 years           | Metastatic colon     | Diarrhea from start | Colonoscopy:     | Loperamide          | Treatment was       |
|                           |         | Adjuvant           | cancer                | of chemotherapy     | terminal ileitis  | Intravenous fluids  | switched to FOLFOX  |
|                           |         | Capecitabine-      |                      |                     | MR enterography:  | Electrolyte         |                     |
|                           |         | oxaliplatin        |                      |                     | distention of the| replacement         |                     |
|                           |         |                    |                      |                     | colon and thickening of the terminal ileal loop | Budesonide         |                     |
|                           |         |                    |                      |                     | DPyD: no mutation |                     |                     |

CT, computed tomography; DPyD, dihydropyrimidine dehydrogenase; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin.