CASE REPORT

Breast cancer, DPYD mutations and capecitabine-related ileitis: description of two cases and a review of the literature

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SUMMARY

Despite many treatment advances, metastatic breast cancer remains an incurable disease and is the third leading cause of cancer-related deaths in Europe. Capecitabine has become a standard treatment option for metastatic breast cancer, as a single agent or in combination. Hand-foot syndrome and diarrhoea are the most frequently reported side effects, while capecitabine-related ileitis is very rare. Deficiency of dihydropyrimidine dehydrogenase activity leads to severe toxicities after administration of 5-fluorouracil or its prodrugs. We report two cases of patients with metastatic breast cancer who developed ileitis after treatment with capecitabine. One patient had a DPYD gene abnormality.

BACKGROUND

Outcome of patients with metastatic breast cancer (MBC) has improved with the regulatory approvals of new therapeutic agents but the goal of treatment remains palliative.¹ While anthracyclines and taxanes have been the mainstay of treatment for many years, data confirmed the efficacy of capecitabine, on oral prodrug of 5-fluoropyrimidine (5-FU) in the treatment of patients with MBC as a single agent,² or in combination.³

Capecitabine is well tolerated, with a favourable safety profile, the most common adverse effects being hand-foot syndrome and diarrhoea.² Small bowel toxicity such as ileitis is an anecdotal finding and has been reported in single case reports (table 1). None of them involve patients diagnosed with breast cancer. However, unusually severe toxic events related to capecitabine have been described in patients with a dihydropyrimidine dehydrogenase (DPD) deficiency, some of which proved to be fatal.⁴ Upfront screening for this deficiency is not recommended since thousands of patients with various solid tumours are treated with 5-FU or its derivatives. The advent of gene sequencing, a technology used increasingly for the identification of genomic aberrations related to cancer genes in order to tailor treatment, might help the identification of patients at risk of excessive toxicity. We report the cases of two patients with MBC, treated with capecitabine who developed treatment-related ileitis. Both patients were genotyped for DPYD (the DPD gene) and a mutation was detected in one of the patients.

CASE PRESENTATION

Case 1

A 66-year-old woman, current smoker, was initially diagnosed as having a large right breast mass measuring 11×7×11 cm on physical examination. A core biopsy revealed infiltrating ductal breast carcinoma that was oestrogen-receptor and progesterone-receptor positive. Immunostains for human epidermal growth factor receptor 2 (HER2)/neu were negative. A subsequent staging bone and CT scans demonstrated distant metastases in the liver. The patient was treated with multiple lines of endocrine therapy and chemotherapy: doxorubicin+cyclophosphamide, paclitaxel+bevacizumab, tamoxifen, fulvestrant and docetaxel. Two weeks after starting capecitabine as fourth-line chemotherapy at a dose of 1250 mg/m² twice daily, she presented to the emergency department with fever, grade 3 diarrhoea, severe performance status alteration, fatigue and emesis.

Case 2

A 67-year-old patient diagnosed with metastatic triple-negative breast cancer presented to our care with chest wall relapse as well as supraclavicular and mediastinal lymph nodes. She had been previously treated with anthracyclines and taxanes in the neoadjuvant setting then paclitaxel+bevacizumab in the metastatic setting. Capecitabine was prescribed in the second-line metastatic setting, but 2 days after starting the second cycle, she was hospitalised with grade 3 diarrhoea, fever, reduced appetite and fatigue.

INVESTIGATIONS

Case 1

Stool cultures were negative, notably *Clostridium difficile*. An abdominal CT was performed and revealed submucosal oedema of the distal ileum with abnormal thickening of its wall. A colonoscopy with biopsy was performed a few days later showing inflammatory changes in the ileal mucosa (figure 1).

Case 2

Stool cultures were negative, notably for *Clostridium*. A plain frontal supine radiograph of the abdomen showed indirect signs of small bowel obstruction. Contrast-enhanced CT of the abdomen revealed parietal thickening of the terminal ileal loop compatible with the diagnosis of ileitis (figure 2).

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Table 1 Ileitis case reports in the literature

	Patients	Clinical description	Diagnostic findings	Management
Case 1 Barton ¹⁴	<ul style="list-style-type: none"> ▶ 54-year-old man ▶ Adenocarcinoma of the right colon ▶ Adjuvant capecitabine 	>Third cycle: severe cramps, diarrhoea	Colonoscopy: ulcerative ileitis with eosinophilic infiltrates	Parenteral nutrition + empiric antibiotherapy
Case 2 Bouma and Imholz ¹³	<ul style="list-style-type: none"> ▶ 73-year-old man ▶ Colon cancer with liver metastases ▶ Palliative chemotherapy: bevacizumab+oxaliplatin +capecitabine 	Abdominal pain, nausea and diarrhoea with subfebrile temperature	CT of the abdomen: bowel wall thickening particularly of the ileum	Adaptative diet +intravenous hydration
Case 3 El Gahmi ¹⁵	<ul style="list-style-type: none"> ▶ 65-year-old man ▶ Metastatic adenocarcinoma of the rectum ▶ Pelvic radiotherapy+XELOX 	>12 days: fever, abdominal pain, vomiting and diarrhoea	<ul style="list-style-type: none"> ▶ Colonoscopy: isolated ulceration in the terminal ileum ▶ Histopathology: eosinophilic infiltrate ▶ The dihydropyrimidine dehydrogenase (DPD) mutation test was negative 	Intravenous antibiotics and fluids
Case 4 Radwan ¹⁶	<ul style="list-style-type: none"> ▶ 67-year-old man ▶ Colon adenocarcinoma ▶ Adjuvant chemotherapy with capecitabine 	>C2: reduced appetite, lower abdominal discomfort, diarrhoea	CT scan+abdominal X-ray: suggestive of an acute ileitis	Rehydration+antibiotics
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Case 5	<ul style="list-style-type: none"> ▶ 66-year-old woman ▶ Metastatic breast cancer ▶ Capecitabine as palliative treatment 	>C1: fever, diarrhoea, fatigue and emesis	<ul style="list-style-type: none"> ▶ Abdominal CT: submucosal oedema of the distal ileum with abnormal thickening of its wall ▶ Colonoscopy with biopsy: eosinophilic infiltrates confirming the diagnosis of ileitis 	Antibiotics
Case 6	<ul style="list-style-type: none"> ▶ 67-year-old woman ▶ Metastatic breast cancer ▶ Second-line palliative setting: capecitabine 	>C2: diarrhoea, fever, fatigue and reduced appetite	<ul style="list-style-type: none"> ▶ DPD mutation: positive ▶ CT scan: parietal thickening of the terminal ileal loop ▶ DPD mutation: negative 	<ul style="list-style-type: none"> ▶ Intravenous wide spectrum antibiotics ▶ Hydration ▶ Bowel rest

C1, first cure; C2, second cure.

DIFFERENTIAL DIAGNOSIS

Case 1

Drug-induced diarrhoea was suspected since it is a commonly described adverse event associated with capecitabine. However, the severity of the clinical presentation with fever pointed to infectious colitis. Stool cultures were however negative and CT scan followed by endoscopy and biopsy confirmed the diagnosis of capecitabine-induced ileitis. This diagnosis was retained because of the timing of the adverse event (2 weeks after starting capecitabine) and in the absence of other contributing factors. Even though this is a rare adverse event, capecitabine-induced ileitis has been described in case reports.

Case 2

This second case was recorded a few weeks after case 1. Once again, infectious colitis and/or capecitabine-induced diarrhoea

Figure 1 Absence of intraepithelial lymphocytic infiltrates in favour of a non-atrophic ileitis (×40).

were suspected but not retained following negative stools cultures and a CT of the abdomen suggesting the diagnosis of ileitis. Capecitabine-induced ileitis was the retained diagnosis because of the timing of the adverse event and the absence of other contributing factors.

TREATMENT

Case 1

Capecitabine was interrupted and the patient received hydration and wide spectrum antibiotics.

Case 2

Capecitabine was discontinued and the patient was treated with intravenous wide spectrum antibiotics, hydration and bowel rest.

OUTCOME AND FOLLOW-UP

Case 1

Signs and symptoms subsided after a few days of hydration and antibiotics and the patient achieved a full recovery. In view of the cataclysmic diarrhoea, the search for a mutation of DPD was positive (DPYD*5,6). Treatment with capecitabine was therefore permanently discontinued. The patient went on a drug holiday and a treatment with exemestane and everolimus was started 4 months later after breast cancer progression.

Case 2

The patient made a full recovery a few days later. The search for a DPD mutation was negative. Another case report described the case of a patient that presented with capecitabine-induced ileitis with successful rechallenge with the drug at a lower dose in the absence of DPD deficiency. However, the treating

Figure 2 CT scan revealing abnormal bowel wall thickening compatible with diagnosis of ileitis.

physician and the patient decided to permanently discontinue capecitabine after this complication.

DISCUSSION

The medical treatment of MBC includes a rapidly growing range of options but chemotherapy remains an important treatment backbone, administered sequentially with endocrine therapy in luminal disease and in combination with anti-HER2 agents in HER2-positive disease.⁵ The treatment is aimed primarily at prolonging progression-free survival and overall survival as well as maintaining quality of life.⁶ No global consensus exists regarding the ideal treatment sequence for MBC, and its choice is guided by a number of factors taking into account the hormone receptor status, HER2 status, sites of metastasis, prior treatment, anticipated side effects and patient preference.⁵ Capecitabine is a valuable treatment option in MBC, and it is approved as a single agent for patients that are resistant to paclitaxel and anthracyclines, and for whom further anthracycline therapy is contraindicated.⁷ Capecitabine is a prodrug that is metabolised to 5-fluorouracil, in a three-step enzymatic process, on absorption from the gastrointestinal tract and is designed to mimic its pharmacokinetics.⁸ Several factors make capecitabine an ideal agent for the treatment of MBC. It holds major advantages such as its oral administration and a good tolerability profile. Hand-foot syndrome (or palmar-plantar erythrodysesthesia) is regarded as the most common adverse event with an incidence of 20–60%.⁹ The next most common side effects are diarrhoea and to a lesser extent, stomatitis. However, adverse events are overcome in the majority of cases by intermittent dose interruptions or dose reductions with resumption at a lower dose if necessary after recovery.^{9–10} Capecitabine monotherapy is a therapeutic option appreciated by physicians because of the generally low toxicity profile including minor myelosuppression, and by patients because it does not cause alopecia,^{11–12} and does not necessitate frequent hospital visits.

However, a small number of patients develop severe and sometimes life-threatening toxicity after standard doses of capecitabine, the majority of which consist in gastrointestinal manifestations, predominantly diarrhoea. These events appear to be dose-dependent and schedule-dependent. Colitis is often described, and to date, small bowel toxicity during capecitabine use has been described in only three published case reports.^{13–16} The diagnosis is based on symptoms including abdominal pain, nausea, diarrhoea and fever, and is often confirmed by CT of the abdomen. This imaging modality shows marked thickening of the wall of the ileum and excludes other diagnoses such as colitis. Obstructions or fistulas

between adjacent loops of the intestine are serious complications of this condition. Treatment consists in capecitabine interruption, an adapted diet, hydration and antibiotics. Surgery can be avoided with this conservative approach. In one case, a rechallenge was possible after the initial interruption of capecitabine.¹³

DPD is a key enzyme in the breakdown of 5-FU, and DPD deficiency is a metabolic disorder in which absent or significantly decreased activity of DPD occurs. It is an important determinant for severe adverse reactions following exposure to 5-FU or the 5-FU oral analogue, capecitabine. Individuals with diminished DPD activity cannot effectively inactivate 5-FU. This leads to toxic levels of 5-FU and to severe to lethal haematological, gastrointestinal or neurological reactions.¹⁷ The advent of new technologies such as next-generation sequencing, and their application in clinical oncology, allows a quicker and more efficient diagnosis of inherited polymorphisms. Indeed, genetic polymorphism in DPYD has shown to be potentially responsible for lethal toxicity after capecitabine-based chemotherapy. The entire DPYD coding region (23 exons including their flanking intronic regions) and the 3' untranslated region can now be sequenced on genomic DNA extracted from peripheral blood cells. This technique can help identify multiple haplotypes, some of which are associated with specific adverse events.¹⁸ Only one of our patients who developed ileitis harboured a DPYD mutation. However, even though a DPYD mutation was excluded, other mutations could still be linked to capecitabine toxicity. Indeed, mutations in TYMS (human thymidilate synthase gene) are associated with up to a 2.5-fold risk of toxicity to 5-FU therapy.¹⁹ While genomic profiling is making its way to the clinic for the tailoring of treatments based on the genomic landscape of patient's tumour,²⁰ the new pharmacogenetic testing methods provided by next-generation sequencing may allow the identification of patients who are at the greatest risk for adverse effects, allowing a more individualised approach to their chemotherapy management.

Learning points

- ▶ Diarrhoea is a well-known adverse event of capecitabine.
- ▶ Capecitabine-induced diarrhoea is very rare but has been described in multiple case reports listed in [table 1](#).
- ▶ Dihydropyrimidine dehydrogenase is a key enzyme in the breakdown of 5-fluoropyrimidine (5-FU).
- ▶ Cataclysmic toxicity (gastrointestinal, mucocutaneous or haematological) with 5-FU or 5-FU derivatives such as capecitabine should lead to the search for dihydropyrimidine deficiency.
- ▶ Dihydropyrimidine deficiency is a contraindication to treatment with 5-FU and certain 5-FU derivatives because of the risk of severe to lethal complications.

Competing interests None.

Patient consent Obtained.

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