Severe enteropathy associated with raltitrexed and oxaliplatin chemotherapy: report of two patients experiencing this rare, potentially lethal gastrointestinal adverse event

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Among the several different combination chemotherapy regimens for the treatment of patients with metastatic colorectal cancer, oxaliplatin plus raltitrexed has shown encouraging therapeutic results and a fairly good toxicity profile. Here, we report on two patients with metastatic colorectal cancer receiving this combination therapy, which leads to severe enterocolitis and neutropenia resulting in death in one patient. One patient was a 67-year-old woman suffering from an adenocarcinoma of the sigmoid colon with multiple liver metastases. The other patient was a 74-year-old woman with colon cancer, and metachronous multiple pulmonal and hepatic metastases. In both patients, palliative chemotherapy consisted of oxaliplatin 130 mg/m^2 in combination with raltitrexed 3 mg/m^2 on day 1 every 21 days. Both patients developed neutropenia in combination with severe enterocolitis after the fourth and the second chemotherapy cycle, respectively. Despite antibiotic treatment, diarrhea persisted in both patients for weeks. One patient died 17 days after hospital admission because of enteric sepsis with bleeding of the colonic mucosa and multiorgan failure. The other patient recovered completely and was discharged from hospital after 8 weeks. Severe enterocolitis, a hitherto infrequently recognized adverse event, which has been described in association with 5-fluorouracil/leucovorin and oxaliplatin chemotherapy, may also occur with raltitrexed and oxaliplatin. Physicians should be aware of this rare, although potentially lethal, gastrointestinal toxicity.
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Introduction

Colorectal carcinoma is one of the most common cancers in western countries and is the second leading cause of cancer deaths after pulmonary malignancies. Within the last few years, because of the availability of new effective compounds, such as the topoisomerase I inhibitor irinotecan, the platinum derivative oxaliplatin, the oral 5-fluorouracil (5-FU) prodrugs and the novel thymidylate synthase inhibitor raltitrexed, objective response rates, and progression-free and overall survival have improved in patients with metastatic colorectal cancer [1,2]. Ongoing clinical trials are investigating innovative chemoimmunotherapeutic strategies and combinations of new drugs. The combination of oxaliplatin and raltitrexed showed encouraging results in preclinical and clinical studies in patients with metastatic colorectal carcinomas, most probably because of different mechanisms of action, supraadditive efficacy and different safety profiles. Phase II studies in patients with chemotherapeutically non-pretreated metastatic colorectal cancer demonstrated objective response rates ranging from 47 to 57% [3–6]. The most common National Cancer Institute Common Toxicity Criteria grade III–IV toxicities among patients treated with this combination were neutropenia, neurotoxicity, diarrhea and transient liver function abnormalities. In the above-mentioned four phase II studies, six out of 232 (2.6%) included patients died because of treatment-related hematological and/or nonhematological toxicities [3–6].

We report here on two patients with metastatic colorectal cancer suffering from fulminant toxic enterocolitis and death in one case, which was associated with combination chemotherapy consisting of oxaliplatin and raltitrexed.

Case report

Case 1

One patient was a 67-year-old woman. The diagnosis of an adenocarcinoma of the sigmoid colon with metachronous liver metastases was made in October 2004, at which time she underwent colonic resection and primary reanastomosis. Palliative chemotherapy consisted of oxaliplatin 130 mg/m^2 in combination with raltitrexed 3 mg/m^2, both given intravenously on day 1 every 21 days.

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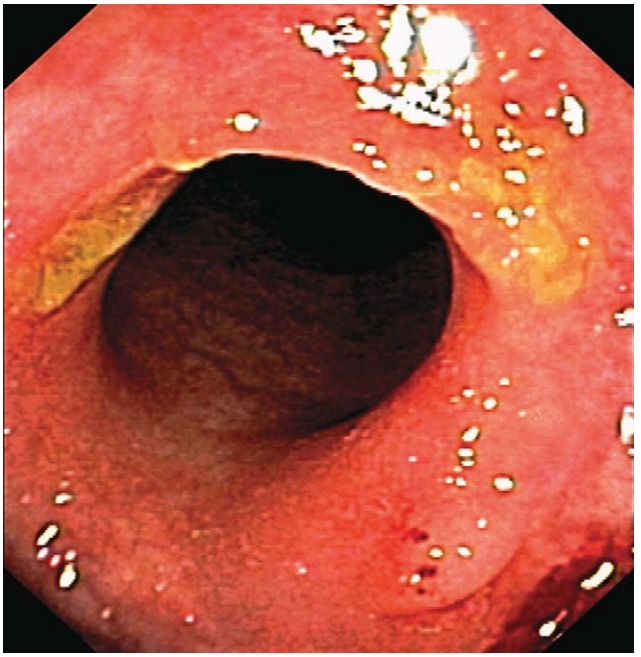
The first three treatment cycles were fairly well tolerated, with nausea (grade 1) and constipation (grade 2) being the only observed side-effects. As a computed tomography reassessment of the abdomen demonstrated stable disease and because of the good tolerance of the treatment, three additional chemotherapy cycles were planned. Seven days after the fourth cycle, in February 2005, the patient experienced severe diarrhea and emesis, and was admitted to the hospital after collapsing at home. She presented with diffuse abdominal pain and diarrhea grade 4. No fever was noted and neither the physical examination nor radiological/sonographic examinations showed any evidence of peritonitis. Initial blood tests revealed pancytopenia with a white blood cell count of 0.54 g/l (normal range: 4.0–10.0 g/l), hemoglobin 7.4 g/dl (normal range: 12.0–16.0 g/dl) and platelet count 53 g/l (normal range: 150–350 g/l), as well as an elevated C-reactive protein of 35.37 mg/dl (normal range: < 1 mg/dl). Both aerobic and anaerobic blood cultures were negative for bacterial growth.

The patient had a history of hypertension and diabetes mellitus. Except for the diagnosis of metastatic colon cancer, there was no history of digestive disorders, previous gastrointestinal symptoms and no family history of inflammatory bowel disease. The patient had not received antibiotics since colonic resection 5 months ago and had not ingested improperly prepared food, raw meat or seafood. No family members experienced coincident digestive dysfunction.

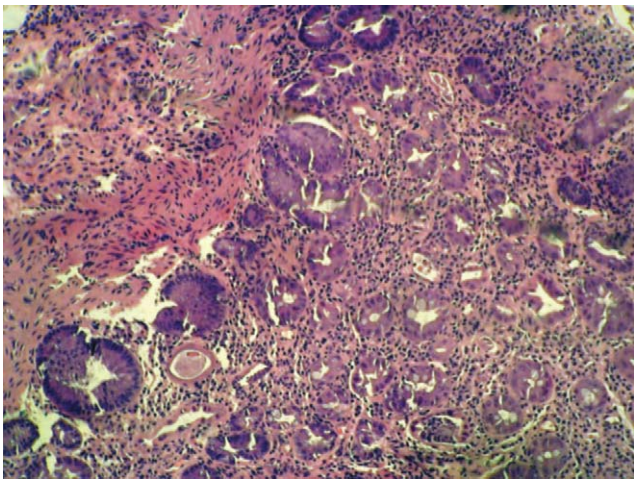
On the day of hospital admission, the patient was empirically treated with metronidazol 1500 mg intravenously once daily. Due to pancytopenia, subcutaneous treatment with granulocyte colony-stimulating factor, 30 MioIE was initiated and two red blood cell concentrates were substituted. Due to continuous diarrhea, antibiotic treatment was modified to ciprofloxacin 400 mg and cefpirom 2 g, both given twice daily. A computed tomography of the abdomen showed enterocolitis, which was endoscopically confirmed; colonoscopy, in fact, showed a severe inflammatory reaction of the mucosa with numerous ulcer lesions (Fig. 1). Histology demonstrated toxic enterocolitis (Fig. 2). Stool examination was negative for parasites and *Clostridium difficile* toxin. Stool cultures were negative for enteric pathogens including *Salmonella*, *Shigella*, *Yersinia*, *Enterobacter* and *Campylobacter* species. Additional therapeutic management consisted of somatostatin (3×0.5 mg/day, subcutaneously), intravenous fluids, total parenteral nutrition and gastrointestinal rest. Still, diarrhea persisted and infection parameters increased. The patient experienced multiorgan failure beginning with renal impairment. She became somnolent and died 17 days after admission to hospital. In the autopsy, the diagnosis of an enteric sepsis in combination with toxic enterocolitis and bleeding of the colonic mucosa was confirmed.

Fig. 1



Colonoscopy after the fourth cycle demonstrating a severe inflammatory reaction of the colonic mucosa with numerous ulcers.

Fig. 2



Histologic analysis of the colonic mucosa showing disturbed mucosal architecture and infiltrating neutrophil granulocytes correlating with a toxic enterocolitis.

Case 2

The other patient was a 74-year-old woman with a history of mucomembranous pemphigoid involving the skin and both eyes, insulin-dependent diabetes mellitus, and breast cancer 9 years ago. An accidentally performed chest X-ray revealed pulmonary metastases and

subsequent examinations demonstrated multiple hepatic metastases too. The histology of one of the liver metastases revealed an affinity to colorectal cancer; a small nonstenosing primary tumor in the left colonic flexura was verified endoscopically, but was left *in situ*. Therefore, the patient received a palliative cytotoxic treatment consisting of oxaliplatin 130 mg/m^2 in combination with raltitrexed 3 mg/m^2 intravenously on day 1 every 21 days. Ten days after the second cycle, in July 2005, the patient developed diarrhea and emesis, and was admitted to the hospital. Initial blood tests showed neutropenia (white blood count 2.62 g/l), hemoglobin 10.4 g/dl, platelet count 316 g/l and an evaluated C-reactive protein of 6.67 mg/dl. As in the previous case, both aerobic and anaerobic blood cultures as well as stool cultures were negative.

On the day of admission, the patient was empirically treated with metronidazol 1500 mg intravenously once daily. Due to neutropenia, the patient was treated with granulocyte colony-stimulating factor subcutaneously. Due to continuous diarrhea, antibiotic treatment was modified to intravenous ciprofloxacin 400 mg twice daily; symptomatic management consisted of intravenous fluids and total parenteral nutrition. In the following weeks, diarrhea persisted, but infection parameters declined. The patient fully recovered and was discharged from hospital after 8 weeks.

Discussion

Over the last few decades, major improvements have been achieved in the treatment of metastatic colorectal cancer. New effective cytotoxic agents and modified 5-FU-based schedules ± biologicals, in fact, have produced much better results than conventional fluoropyrimidine treatment [1,2,7]. Gastrointestinal and hematologic toxicities as well as mucositis are commonly associated with 5-FU-based therapy [8]. It is well known that 5-FU toxicity varies with dose, schedule and route of administration. Some speculation has also existed about sex-related differences in treatment tolerance, particularly in the case of 5-FU-based therapy [8]. This phenomenon can probably be explained by the decreased clearance of the antimetabolite in women due to differences in dihydropyrimidine dehydrogenase activity. Evaluations of the toxicity of 5-FU-based studies suggest a higher incidence rate of adverse reactions in women than in men with respect to hematological toxicities, mucositis and, sometimes, diarrhea [8,9].

We report here on two female patients with metastatic colorectal cancer receiving a palliative chemotherapy with oxaliplatin in combination with raltitrexed, which led to severe enterocolitis and neutropenia, that resulted in the death of one patient. The pathogenesis of neutropenic enterocolitis starts with mucosal damage and consecutive increased proliferation of bacterial growth resulting from both this damage and the decreased immunocompetence of the patients. The production of bacterial endotoxins leads to intramural hemorrhage, ulceration and ischemia. In some cases, necrosis of the bowel followed by consecutive proliferation can occur. The most common National Cancer Institute Common Toxicity Criteria grade III–IV toxicities in four phase II trials [3–6] using this combination treatment were neutropenia, neurotoxicity, liver function abnormalities and diarrhea independent of the oxaliplatin dose, which was 100 mg/m^2 in two studies [5,6] and 130 mg/m^2 in the other two [3,4]. Seitz *et al.* [3] reported four patient deaths, which were possibly related to the trial treatment. Two of these lethal complications, one due to severe neutropenia and the other due to diarrhea, were definitively related to treatment, whereas the other deaths were classified as possibly related to treatment (hepatic dysfunction and laryngeal diplegia in one patient each). Douillard *et al.* [6] observed two treatment-related deaths. In a previously published phase II trial we observed no toxic death, but we had to reduce the dose of both cytotoxic drugs in 12% of the patients because of severe diarrhea in three (female) patients, emesis in one patient, and combined severe gastrointestinal and hematotoxicity in one patient [4]. Cascinu *et al.* [5] reported a 25% dose reduction of both cytotoxic drugs in three patients because of severe (grade 4) transaminitis or diarrhea. Unfortunately, we were unable to figure out sex-related differences in toxicity in three of four clinical trials, because data have not been reported.

In conclusion, the combination chemotherapy of oxaliplatin and raltitrexed has shown encouraging therapeutic results in the treatment of metastatic colorectal cancer, resulting in an objective response of 47–57%. Nevertheless, severe enterocolitis, a hitherto infrequently recognized adverse event, may occur independent of the schedule including raltitrexed and oxaliplatin. With vigilant monitoring and early identification of signs and symptoms such as abdominal cramps, fever and weakness, particularly in the case of female patients, and early initiation of aggressive therapy on the basis of the recommended guidelines for treatment-induced diarrhea [10], this potentially lethal gastrointestinal toxicity can probably be avoided and/or its clinical manifestations alleviated.

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