Gastrointestinal toxicity associated with weekly docetaxel treatment

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Previous studies have demonstrated a marked reduction of haematological and non-haematological toxicity if weekly doses of docetaxel <40 mg/m2 were used. Reviewing the literature, neutropenic enterocolitis is uncommon but not unknown in patients treated with taxane-based chemotherapy. Although this complication occurs rarely, here we report on two patients, one with metastatic breast cancer and one with non-small-cell lung cancer, treated on a weekly schedule with single-agent docetaxel. Both patients developed excessive and fatal haemorrhagic gastroduodenitis and enterocolitis associated with grade 2 and 3 neutropenia. We would like to stress the importance of symptoms such as abdominal pain and tenderness, fever, diarrhoea and mucositis, with or without neutropenic fever, in patients treated with docetaxel-based chemotherapy. These symptoms should alert the physician and supportive care management should be started aggressively and immediately.

Key words: chemotherapy, docetaxel (Taxotere®), neutropenic enterocolitis

Introduction

Docetaxel (Taxotere; Aventis, Bad Soden, Germany) has demonstrated high anti-tumour activity in different solid tumours. When docetaxel is administered at a dose of 100 mg/m2 every 3 weeks, 70–90% of patients develop grade 3/4 neutropenia [1–3]. However, previous analyses have demonstrated a marked reduction in haematotoxicity when docetaxel is administered in a weekly schedule [4, 5]. In phase I/II studies, the recommended dose for the weekly schedule was between 35 and 45 mg/m2, and haematological and non-haematological toxicity grade 3/4 was uncommon if doses <40 mg/m2 were used [4–16].

Generally, neutropenic enterocolitis is a rare but severe side-effect of cytotoxic treatment. Previous investigators have reported cases of metastatic breast cancer (MBC) treated with doses of 60–90 mg/m2 docetaxel who developed clinical signs of severe enterocolitis [17].

The sequence of events in neutropenic enterocolitis has been proposed as follows: mucosal damage of the bowel, bacterial invasion, increased proliferation of bacteria resulting from decreased immunocompetence (neutropenia), production of bacterial endotoxins, intramural haemorrhage, ulceration, ischaemia, and in some cases, necrosis of the bowel wall and perforation [18].

Case reports

Case 1

A 81-year-old female was diagnosed with MBC (disease sites: lung, bone, liver) in July 1999. The patient was started on a hormonal therapy with tamoxifen and arimidex. Owing to progression of disease in February 2000, an orally administered chemotherapy consisting of capecitabine (Xeloda®) was started (one cycle, 8–21 February 2000, 1500 mg orally, twice daily), and was well tolerated.

Since rapidly rising tumour markers and progressive dyspnoe must be diagnosed, single-agent docetaxel on a weekly schedule (35 mg/m2) was begun with dexamethasone prophylaxis (six 8 mg doses, orally, every 12 h, beginning 12 h before treatment). The first cycle was given on 9 March 2000 and was well tolerated; therefore, therapy was continued...
and carcinoembryonic antigen (CEA) serum level decreased continually (3 March: 51.1 ng/ml; 16 March: 30.8 ng/ml; 20 March: 25.2 ng/ml). On 20 March the patient was hospitalised due to severe dysphagia, epigastric pain and non-febrile neutropenia (leucocyte count 1.7 g/l). A gastroduodenoscopy was performed and showed severe erosive esophago-gastro-duodenitis, which was treated with omeprazol, fluconazol and piperacillin/combactam. Owing to neutropenia, the patient received granulocyte colony-stimulating factor (G-CSF; 300 µg s.c. daily). Two days later the patient developed severe haemorrhagic diarrhoea, and metronidazol was added. All microbial testings were negative, including for Clostridium and Clostridium toxin.

Despite broad-spectrum antimicrobial and maximum supportive therapy, the patient suffered from progressive haemorrhagic diarrhoea and therefore a recto-sigmoidoscopy was performed on 20 March, which showed marked haemorrhagic colitis. One day later the patient developed acute renal failure and died of multi-organ failure on 29 March 2000.

### Case 2

A 72-year-old male was diagnosed with stage IV non-small-cell lung cancer (NSCLC) in January 2000 (disease sites: pleural, lung, bone). Single-agent gemcitabine chemotherapy was begun (1000 mg/m², given on days 1, 8 and 15, repeated every 4 weeks), which was well tolerated and was given until disease progression was noted. Owing to bone metastases the patient also received pamidronate.

On 23 March 2000, the patient was started on a weekly schedule of docetaxel (35 mg/m²) with routine corticosteroid prophylaxis. The patient received three cycles (23 March, 30 March and 6 April) of docetaxel, which were all well tolerated, and the tumour markers declined slowly. One week later the patient suffered epigastric pain and reported haemorrhagic vomiting. The blood sample showed grade 2 neutropenia (leucocyte count 3.1 g/l). A gastroduodenoscopy was performed, which detected severe haemorrhagic esophago-gastro-duodenitis; treatment with omeprazol was therefore begun. Five days later the patient, still suffering from abdominal pain, developed septic temperatures, dyspnoe and haemorrhagic diarrhoea. Broad-spectrum antimicrobial therapy was started. Despite maximum therapy, the patient died of multi-organ failure on 27 April 2000.

### Discussion

Weekly administration of docetaxel is an effective regimen with low toxicity in MBC and other solid tumours. In heavily pre-treated or elderly patients, where intensive chemotherapy is no longer feasible, the weekly administration of docetaxel appears to provide an alternative therapy with high efficacy and low toxicity. The low rate of severe side effects associated with a weekly schedule may also permit a combination of docetaxel with other cytotoxic agents, such as vinorelbine [19, 20].

The weekly schedule combines the advantages of a higher dose intensity compared with the recommended dose of 75 mg/m² every 3 weeks for heavily pre-treated patients, as well as a marked reduction in haematotoxicity [4–16]. Moreover, the short duration of drug application (30 min) clearly supports outpatient use of this regimen.

Previous phase I/II studies indicated that severe neutropenia (grade 3/4) could largely be prevented by keeping weekly doses to <40 mg/m². In several studies, grade 3 haematotoxicity occurred in 5% of patients and grade 4 haematotoxicity in 1% of patients (grade 3/4 range 0–12.5%). Grade 3/4 non-haematological toxicity has been observed in 18% of patients, including alopecia (10%), fatigue and asthenia (1%), skin and nail toxicity (1%), and mucositis (2%) [4–16].

As described previously, docetaxel may result in an inflammatory bowel syndrome that clinically mimics pseudomembranous colitis, even when given as single-agent therapy or in combination with other cytotoxic agents, such as vinorelbine [17]. The syndrome results in acute abdominal pain, possibly associated with neutropenia, fever, haemor-
rhagic diarrhoea and mucositis (or a combination of these symptoms), and should alert the physician to the possibility of pancolitis. In the patients described by Ibrahim et al. [17], two of six patients died, despite prompt and aggressive management, due to neutropenic enterocolitis, but both patients were treated with a combination of docetaxel (75 mg/m², day 1) and vinorelbine (20 mg/m², days 1 and 5, repeated every 3 weeks). One patient who developed neutropenic fever was treated with single-agent docetaxel (75 mg/m²) and underwent emergency laparotomy due to acute abdominal pain and a pneumoperitoneum on day 29 of the cycle when she was not neutropenic. The patient survived.

Kreis et al. [20] reported that they suspected docetaxel might induce more bowel damage when given with a second anti-tubulin agent, such as vinorelbine. Setzer et al. [18] emphasised the importance of neutropenia as a general risk factor for mortality, since both patients reported by Ibrahim et al. [17] who died had developed neutropenia.

Unlike the patients reported by Ibrahim et al. [17], our patients were treated with single-agent docetaxel on a weekly schedule (35 mg/m²), and only one patient developed grade 3 neutropenia, which was of short duration. In several published studies concerning weekly administration of docetaxel as a single agent or in combination therapy, no case reported enterocolitis [4–16]. In a study including 130 patients with weekly docetaxel for MBC, we observed no severe gastrointestinal complications (unpublished data).

Li et al. [21] reported a retrospective analysis of all breast cancer patients treated with taxan-based chemotherapy (TBC) at the Twenty-third Annual San Antonio Breast Cancer Symposium. Of 835 patients treated with TBC, 63 patients resulted from TBC-induced gastrointestinal complications (7.5%), including seven patients who suffered from bloody diarrhoea. Of 10 patients given docetaxel-based chemotherapy and four given paclitaxel-based chemotherapy, there were 16 admissions with a diagnosis of colitis, presenting with abdominal pain in combination with other symptoms. One patient died with ulcerations in the colon. No recurrence of colitis was observed when TBC was discontinued.

Interestingly, Ibrahim et al. [17] reported one patient who developed transmural necrosis associated with perforation of the bowel after treatment with docetaxel (90 mg/m², every 3 weeks) and pamidronate for MBC. This patient was not neutropenic when the complication developed, and the patient survived and recovered completely after surgical intervention. The male patient in our case report also received a combination of docetaxel and pamidronate, and showed only mild neutropenia when suffering from haemorrhagic pancolitis. In the literature it appears that this complication occurs rarely when docetaxel is given on a weekly schedule.

References

