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Neutropenic Enterocolitis in an Advanced Epithelial Ovarian Cancer Patient Treated with Paclitaxel/Platinum-based Chemotherapy: A Case Report and Review of the Literature

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Abstract. *Background: Literature data show that neutropenic enterocolitis is a rare but severe complication that can occur in cancer patients treated with chemotherapy and especially with taxanes. Case Report: A 60-year-old woman with stage IIIc epithelial ovarian cancer developed neutropenic fever, abdominal pain, severe diarrhoea, nausea, vomiting and oral mucositis one week after the first postoperative cycle of paclitaxel (175 mg/m^2 3-hour infusion) plus carboplatin-based chemotherapy. Abdominal X-ray showed diffuse dilatation of the ileal and colonic loops with air/fluid. The patient soon recovered after intensive supportive care. For the second cycle the dose of paclitaxel was reduced by 20%, but nine days later the patient again developed severe neutropenia with fever, abdominal colicky pain, diarrhoea and vomiting. The culture of blood samples collected on admission was found to be positive for Escherichia coli, whereas stools resulted negative for both enteric rods and Clostridium difficile toxin. The patient recovered with intensive supportive care, and chemotherapy was continued with single-agent carboplatin. Discussion: The increasing use of paclitaxel in first-line as well as in the salvage treatment of epithelial ovarian cancer could increase the occurrence of neutropenic enterocolitis in patients with this malignancy. The importance of symptoms such as neutropenic fever, abdominal pain and tenderness and severe diarrhoea should be stressed in patients who receive taxane-based chemotherapy, and intensive supportive care management should be started immediately.*

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Some chemotherapeutic drugs have been found to be associated with gastrointestinal emergencies (1-11). Neutropenic enterocolitis is a necrotizing inflammation of the bowel that more typically occurs in patients with haematological malignancies who have had long-term neutropenia (6, 9, 10, 12). For instance, Camera *et al.* (10) reported the development of neutropenic enterocolitis in 10 (9%) out of 115 patients with acute myeloid leukaemia, who had received intravenous standard dose cytarabine-containing induction regimens. This complication was lethal in 4 out of 10 patients. Fatal neutropenic enterocolitis has also been observed in a patient undergoing autologous bone marrow transplantation for non-Hodgkin's lymphoma (6). Although it is uncommon in solid tumor patients, in whom treatment-related neutropenia is generally of brief duration (13, 14), neutropenic enterocolitis has sometimes been reported in patients with lung, breast, gastric, ovarian or peritoneal malignancies after treatment with vinorelbine (8, 15, 16), gemcitabine (11) and, especially, with taxanes (15, 17-32). It is worth noting that a review of autopsy files of 4 patients who had received paclitaxel showed mitotic arrest and necrosis in the epithelia of the gastrointestinal tract (33). These phenomena could be associated with bundling of intermediate filaments and could be to due to paclitaxel-induced accumulation of polymerized microtubules.

We describe the case of an epithelial ovarian cancer patient who developed neutropenic enterocolitis during early chemotherapy with a paclitaxel/ carboplatin-based regimen, but who completely recovered after appropriate intensive management.

Case Report

A 60-year-old woman was referred to our Department after bilateral salpingo-oophorectomy, total hysterectomy, douglassectomy, omentectomy and pelvic and para-aortic node sampling for FIGO stage IIIc, moderately- differentiated

serous carcinoma of the left ovary. The residual disease after initial surgery was less than 1cm. The past medical history of the patient included a renal tuberculosis at the age of 20 years and one episode of cerebral ischemia at the age of 55 years, probably due to cardiac embolism associated with chronic atrial fibrillation. The patient routinely received oral anticoagulant, antiarythmic and β-blocker drugs. On admission to our Department, the patient was in good general condition with an ECOG performance status of 0. Blood cell count and chemistry were in the normal range (with the exception of coagulation tests altered by the oral anticoagulant treatment). An echocardiogram revealed a normal left ventricular ejection rate and the glomerular filtration rate, determined by the radioisotope method, was found to be 57 ml/min. Physical and gynaecological examination as well as abdominal-pelvic ultrasound showed no evidence of disease, but the serum CA 125 level was 564 U/ml. Forty days after surgery, the patient received the first cycle of combination chemotherapy consisting of paclitaxel 175 mg/m^2 (three-hour infusion) plus carboplatin at the dose corresponding to an area under the curve (AUC) of 6 mg/ml/min. One week later, the patient was admitted to the hospital because of the onset of fever, abdominal pain, severe diarrhoea, nausea, vomiting and oral mucositis. A blood cell count revealed a grade IV leukopenia and neutropenia and abdominal X-ray showed diffuse dilatation of the ileal and colonic loops with air/fluid. Blood cultures were negative for all microrganisms tested. The patient received wide-spectrum antibiotics, antimicotic drugs, recombinant human granulocyte-colony stimulating factor (G-CSF) and aggressive supportive care, and, within three days, the fever and gastrointestinal symptoms had disappeared, the abdominal X-ray became normal and the leukocyte and granulocyte count rapidly rose to the normal range.

Twenty-one days after the first cycle, the patient received the second cycle of chemotherapy. The serum CA 125 level had decreased to 74 U/ml. The dose of paclitaxel was reduced by 20%, whereas the dose of carboplatin was unchanged. Nine days later, the patient again developed fever, severe neutropenia, abdominal colicky pain, severe diarrhoea and vomiting. Abdominal X-ray and ultrasound revealed dilatation and thickening of the intestinal loops. On admission, blood and stool samples were collected for bacteriological examinations. The patient again received wide-spectrum antibiotics, antimicotic drugs, G-CSF and aggressive supportive care, and within three days, the clinical, laboratory and radiological findings had returned to normal. The culture of blood samples collected on admission was found to be positive for *Escherichia coli*, whereas stools resulted negative for both enteric rods and *Clostridium difficile* toxin. Paclitaxel was deleted from the chemotherapy regimen, and the patient received seven cycles of single-agent carboplatin AUC 6 every three weeks. The serum CA 125 level declined below 35 U/ml before the second cycle of single-agent carboplatin.

At the end of chemotherapy, physical and gynaecological examination, chest X- ray, abdominal-pelvic ultrasound and CT scan showed no evidence of disease, and the serum CA 125 level was still in the normal range. The patient was strictly followed with clinical, serological and ultrasound examinations.

Five months after the last cycle of carboplatin, the serum CA 125 level began to rise (47 U/ml) and doubled within four weeks. Physical and gynaecological examination as well as chest X-ray were still negative, but the abdominal-pelvic CT scan showed a round mass larger than 2 cm in the right pelvis near the lateral wall of the sigmoid colon, associated with right hydroureteronephrosis. The patient underwent laparotomy that confirmed the presence of a pelvic recurrence infiltrating the sigma and the right ureter without any other macroscopic lesion in the abdominal cavity. The pelvic recurrence was resected with concomitant left colectomy and end-to-end colon-rectal anastomosis by staplers and with partial resection of the right ureter and end-to-end ureter-ureteral anastomosis. Multiple random biopsies from paracolic gutters were collected. No macroscopic residual disease was present at the end of surgery. The histological examination of the surgical samples revealed a poorly-differentiated carcinoma of ovarian origin involving the sigma and right ureter. All the nine perisigmoid lymph nodes were metastastic, whereas the biopsies of the paracolic gutters were negative.

The patient started a second-line chemotherapy consisting of single-agent pegylated liposomal doxorubicin 50 mg/m^2 as one-hour infusion, but within two months she developed distant metastases (brain, liver) that rapidly led to her death.

Discussion

Neutropenic enterocolitis is a necrotizing inflammation of the bowel that can rarely occur after chemotherapy in cancer patients. Clinically this complication presents with neutropenic fever, abdominal pain, rebound tenderness and severe diarrhoea that may be bloody (2, 12, 15, 20, 25, 30, 31). Radiological investigations can show paralytic ileus and thickening of the colon wall (9, 25, 30, 34). Aerobic gram-negative septicemia is a common feature (30, 35). Neutropenic enterocolitis has been reported following treatment with different chemotherapeutic agents, including taxanes (8, 11, 15-32). This complication, that occurs in about 0.1% of taxane-based chemotherapy cycles (25), may be due both to a direct effect of the drug on the gastrointestinal epithelium and to a synergistic interaction between taxane-induced mitotic arrest and a compromised bowel (20, 33). In 1993, Seewaldt *et al.* (17) first reported a bowel perforation following paclitaxel chemotherapy in a heavily pre-treated ovarian cancer patient. In the same year,

Pestalozzi *et al.* (18) described 2 cases of typhlitis in metastatic breast cancer patients after the first cycle of combination chemotherapy with paclitaxel (180 mg/m^2) and doxorubicin (75 mg/m^2) given simultaneously as 72-hour continuous infusions. Ibrahim *et al.* (15) reported the occurrence of an ischemic colitis in 6 patients treated with docetaxel-based therapy, 3 of whom were enrolled in a phase I study designed to establish the maximum tolerated dose of the combination of docetaxel and vinorelbine with the prophylactic use of G-CSF. Following paclitaxel-based chemotherapy, 3 and 7 cases of gastrointestinal necrosis have been described by Rose and Piver (19) and Seewaldt *et al.* (20), respectively. This complication occurred 5 to 16 days following the first cycle of chemotherapy. In the series of Seewaldt *et al.* (20), the most common clinical symptoms and signs at presentation were fever (7/7 patients), neutropenia (6/7 patients) and abdominal pain (6/7 patients). In the literature, the mortality of necrotizing enterocolitis ranged from 0 to 57% (15, 19, 20, 25, 32).

Stemmler *et al.* (30) reported the development of fatal haemorrhagic gastroduodenitis and enterocolitis associated with moderate-severe neutropenia in 2 patients, one with metastatic breast cancer and one with non-small cell lung cancer, treated with single-agent docetaxel given weekly. Kouroussis *et al.* (25) observed 5 cases of acute neutropenic enterocolitis complicating taxane-based chemotherapy in a 34-month period during which 4,600 cycles of paclitaxel- or docetaxel-based chemotherapy were given to 800 cancer patients. In these 5 patients, neutropenic fever, abdominal pain, rebound tenderness and severe diarrhoea occurred 7 to 10 days after treatment, and 2 of them had a septic shock. Abdominal CT scan showed a thickening of the colon wall and a pericolic edema, and sometimes a pericolic abscess. All patients were successfully treated with broad-spectrum antibiotics and G-CSF. Li *et al.* (32) reported gastrointestinal complications requiring hospitalisation in 64 of the 1,350 patients who received taxane-based chemotherapy. Neutropenia and/or fever accounted for 56 of these admissions, and 14 patients were diagnosed as having colitis. Abdominal-pelvic CT was abnormal for the 10 patients tested, whereas only 3 of the 9 patients who underwent abdominal X-ray had abnormal findings. Blood cultures were positive in only 3 patients, and all 8 patients tested for *Clostridium difficile* toxin were negative.

In our patient, both clinical and radiological findings supported the diagnosis of acute neutropenic enterocolitis, and the early detection and aggressive management led to a complete recovery. The dose reduction of paclitaxel in the second cycle did not prevent the development of this complication, in contrast to the experiences reported by Li *et al.* (32), and therefore the administration of the taxane was stopped. Patients who develop severe diarrhoea following chemotherapy should be evaluated for *Clostridium difficile* (24, 28, 32, 36, 37), but, in our case, stools resulted negative for its toxin. Conversely, the culture of blood samples collected at the second admission was found to be positive for *Escherichia coli*.

Paclitaxel-platinum- based chemotherapy is currently accepted as the standard regimen for advanced epithelial ovarian cancer, achieving a clinical complete response rate of 50% approximately, a pathological complete response rate of 25-30%, a median progression-free survival of 15.5-22 months, and a median overall survival of 31-44 months (38-44). Moreover, paclitaxel is often used as salvage treatment after first-line platinum-based or paclitaxel-platinum- based chemotherapy (45-49). Thus, the increasing use of paclitaxel in first-line as well as in the salvage treatment of epithelial ovarian cancer could increase the occurrence of neutropenic enterocolitis in patients with this malignancy. The importance of symptoms such as neutropenic fever, abdominal pain and severe diarrhoea should be stressed in patients who received taxane-based chemotherapy, and intensive supportive care management should be started immediately (30).

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