Neutropenic enterocolitis and docetaxel neoadjuvant chemotherapy

Introduction

Neutropenic enterocolitis (NE, typhlitis) is a rare complication of intensive chemotherapy, and though it is more often observed in leukemia and lymphoma, there are a few reported cases of patients with lung cancer [1], hormone-refractory prostate cancer [2] and metastatic breast cancer [3]. Docetaxel, a taxane-based compound, has been proven to be a very effective treatment with acceptable toxicity in breast cancer [4]; it also increases the efficiency of neoadjuvant therapy when combined with doxorubicin and cyclophosphamide (AC) [5].

We report here a unique case of NE in a young, healthy patient with locally advanced breast cancer who received such a regimen.

case report

A 45-year-old woman with no past medical history was referred to our clinic by her family doctor for a breast mass the patient had felt for over a year. On examination of the lower inner quadrant of her right breast, we discovered a 3-cm irregular mass with cutaneous and axillary involvement. The mammogram, an ultrasound and a magnetic resonance imaging documented a 3-cm spiculated mass with calcifications. The stereotactic core biopsy confirmed invasive lobular carcinoma grade III/III, positive for estrogen and progesterone receptors and negative for Her-2 Neu. In this context of T4N1M0 breast cancer, she started a preoperative four-cycle chemotherapy with doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 21 days, that would be followed upon completion by four cycles of docetaxel (100 mg/m²).

Sixteen days after the first treatment, the patient came to our emergency department complaining of fatigue and shivers. Upon evaluation, she was neutropenic (800 k/µl) but despite extensive investigations, no source of infection was found. Since the patient was afebrile and asymptomatic, she was discharged with prophylactic antibiotherapy. The following cycles were well tolerated. Twenty-one days after her last AC treatment, the patient received docetaxel (100 mg/m²) in a 1-h infusion.

Ten days later, the patient consulted in the morning at the oncology clinic for increasing diffuse abdominal pain, nausea and fever up to 39.5°C. She experienced no other gastrointestinal, respiratory and urinary symptoms. Slight pain was elicited upon abdominal palpation as well as slight guarding; however, bowel sounds were present. The blood work showed severe neutropenia (100 k/µl) and leukopenia (400 k/µl). Upon these results, the patient was immediately admitted and received i.v. cefazidime as well as s.c. granulocyte colony-stimulating factor (G-CSF).

A few hours later the patient complained of increasing abdominal pain with no associated symptoms. Ciprofloxacin and metronidazole were administrated; however, the patient rapidly deteriorated presenting severe hypotension, tachycardia as well as localized right lower quadrant rebound tenderness. A computed tomography (CT) scan was carried out and demonstrated moderate quantities of ascites with signs of ileocolitis particularly significant in the right colon, the cecum and the distal ileum. The possibility of ischemic colitis was excluded. Upon these findings and the patient’s fulminant deterioration, an emergency exploratory laparotomy was carried out and revealed a necrotic cecum. The patient underwent a right hemicolectomy and end ileostomy. The histopathological analysis was compatible with neutropenic colitis.

The patient developed postoperative septic shock and disseminated intravascular coagulation. With aggressive intensive care she recovered and was discharged after 16 days.

The neoadjuvant chemotherapy she had received was successful in significantly reducing the size of the tumor to 1.5 cm, but no further treatments were given. Six weeks later, the patient underwent a right breast lumpectomy with axillary dissection and the postoperative course was uneventful.

discussion

NE also known as necrotizing enterocolitis and typhlitis is a rare yet severe complication of chemotherapy. Although some cases have been reported after intensive docetaxel therapy alone, the great majority occurs when it is used in conjunction with other microtubule-targeting agents such as vinorelbine or cyclophosphamide [3, 5]. Such regimens do produce myelosuppression and neutropenia, especially when administered in continuous infusions [1]; however, this effect is usually short lived and of no significant consequence.

There is a single previously reported case of NE under a 21-day cycle of docetaxel alone. The dose was, however, smaller and was used in the treatment of metastatic breast cancer [3]. Our case is the first reported one of NE in a young otherwise
healthy patient with locally advanced breast cancer but no metastases under neoadjuvant taxane-based chemotherapy.

Despite the controversy surrounding the direct role played by the chemotoxic agent in the pathophysiology of NE, ischemic necrosis is believed to be the triggering factor, followed by bacterial invasion in the context of severe neutropenia [1, 6]. Notwithstanding two reported cases of non-neutropenic necrotizing colitis, the most important risk factor of morbidity and mortality seems to be neutropenia. Indeed, the combination of the two is deadly in 40%–50% of cases [2, 7].

There are no randomized trials or prospective studies addressing the management or treatment of NE. Many clinicians follow the guidelines for febrile neutropenia proposed by the Infectious Diseases Society of America [7]. The more conservative approach consists of aggressive fluid resuscitation, bowel rest, broad antibiotic coverage and frequent imaging with the CT scan being the technique of choice [8]. The guidelines also suggest the advantage of using G-CSF in neutropenic patients with sepsis or shock [9]. Laparotomy is indicated in cases of peritonitis, persistent gastrointestinal bleeding despite improvement of neutropenia, thrombocytopenia and coagulopathy and if the patient deteriorates despite aggressive medical therapy [10].

**conclusion**

Our patient had an atypical presentation and the initial complaint was only slight abdominal pain which rapidly deteriorated into peritonitis and associated shock. It is important for physicians to be attentive to seemingly harmless symptoms even in younger patients under aggressive chemotherapy. They may be the only heralding signs of deadly yet preventable complications especially when associated with neutropenia.

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